Practical Guidance for the Evaluation and Management of Drug Hypersensitivity: Specific Drugs

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INTRODUCTION

Allergists and clinical immunologists around the world are increasingly faced with the task of addressing drug allergy and hypersensitivity due to the increase in drug reactions. Furthermore, this is often required to maintain patients on first-line therapies, including antibiotics for those with cystic fibrosis, chemotherapeutic agents for those with cancer, and mAbs for patients with chronic inflammatory diseases. The endeavor assumes minor risks

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such as urticaria and major risks that include anaphylaxis and Stevens-Johnson syndrome. Most of the time these must be addressed without navigation tools or clear algorithms for the mechanisms of reactions. There are few standardized skin tests/*in vitro* tests for diagnosis and rare validated desensitization protocols. Drug testing and desensitization should be considered on the basis of consensus reports (International Consensus [ICON], International Collaboration in Asthma, Allergy and Immunology [ICALL], Practical Allergy [PRACTALL]) as well as practice parameters. However, new and targeted drugs that better address diseases in a precise and personalized fashion are emerging rapidly, and they induce new, unpredictable, and poorly understood reactions. This publication was born out of a grassroots need to provide the seeds of a new discipline: the understanding, diagnosis, management, and treatment of drug allergy and hypersensitivity as a practical clinical endeavor.

Dr Thomas Fleisher embraced this as his presidential theme, as mentioned in the Introduction section of this supplement. In the General Concepts article in this supplement, Drs Ana Dioun Broyles, Aleena Banerji, and Mariana Castells provided the foundational steps in describing the phenotypes, endotypes, and biomarkers of drug reactions, amplifying the Gell and Coombs classification and providing practical algorithms for the diagnosis and management.[1] The lead authors next consulted drug hypersensitivity experts from around the world to precisely define specific drugs and/or drug classes regarding the phenotypic presentations of reactions, diagnostic tools such as skin testing, *in vitro* testing, and challenges, and the best management and treatment approaches including desensitization. The numerous authors who contributed to this section of the supplement have provided the most current information on and the standards for *in vitro* and *in vivo* testing and desensitization procedures when these exist. Their efforts have resulted in an accurate compilation of drug hypersensitivity procedures data that can be applied in a personalized fashion to each drug-allergic patient.

The hope is that this supplement will provide a user-friendly instrument that will be used in clinics, hospitals, wards, and the emergency department on a daily basis, and that its principles will guide and increase allergist immunologists' skills and level of comfort with a practical approach to drug hypersensitivity. The application of the standards described here should help streamline the clinical practice of drug hypersensitivity and provide the most updated and safe care to all patients with drug hypersensitivity. It is also hoped that his resource will be updated every 2 to 3 years with new developments that arise in the diagnosis and management of drug hypersensitivity so as to continue to improve the quality and safety of care.

ANTIMICROBIAL AGENTS

Penicillins (by Timothy Lax, MD, and Antonino Romano, MD)

General. Penicillins are commonly used to treat infections caused by both gram-negative and gram-positive organisms. Penicillin allergy is one of the most commonly reported drug allergies, with a prevalence of 5% to 10%.[2,3] The reported prevalence is higher among hospitalized patients, at 11% to 15%.[4,5] Individuals with a history of penicillin hypersensitivity are more likely to receive alternative antibiotic therapy, which can lead to added expense,

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Abbreviations used

ACD- Allergic contact dermatitis
ADR- Adverse drug reaction
AERD- Aspirin-exacerbated respiratory disease
AGEP- Acute generalized exanthematous pustulosis
ART- Antiretroviral
BAT- Basophil activation test
COPD- Chronic obstructive pulmonary disease
COX- Cyclooxygenase
CYC- Cyclophosphamide
CYP450- Cytochrome p450
DHR- Delayed hypersensitivity reaction
DMCD- Direct mast cell degranulation
DRESS- Drug rash (or reaction) with eosinophilia and systemic symptoms
EAACI- European Academy of Allergy and Clinical Immunology
EGFR- Epidermal growth factor receptor
EMB- Ethambutol
ENDA- European Network of Drug Allergy
FDA- Food and Drug Administration
HCV- Hepatitis C virus
HIT- Heparin-induced thrombocytopenia
HMW- High molecular weight
IDT- Intradermal test
IM-ADR- Immunologically mediated adverse drug reaction
INH- Isoniazid
LA- Local anesthetic
LMWH- Low-molecular-weight heparin
MM- Multiple myeloma
MTX- Methotrexate
NMBA- Neuromuscular-blocking agent
NSAID- Nonsteroidal anti-inflammatory drug
PH- Progestogen hypersensitivity
PI- Protease inhibitor
PPI- Proton pump inhibitor
PPL- Penicilloyl-polylysine
PT- Prick test
PZA- Pyrazinamide
RCM- Radiocontrast media
RMS- Red men syndrome
SCAR- Severe cutaneous adverse reaction
SJS- Stevens-Johnson syndrome
SMZ-TMP- Sulfamethoxazole-trimethoprim
SPT- Skin prick test
TB- Tuberculosis
TEN- Toxic epidermal necrolysis
TKI- Tyrosine kinase inhibitor
UFH- Unfractionated heparin
vWD- von Willebrand disease

lengthened hospital stays, and increased risk for resistant organisms such as vancomycin-resistant *Enterococcus*, *Clostridium difficile*, and methicillin-resistant *Staphylococcus aureus*.[6,7] Despite the frequency of reported allergy, avoidance of penicillin is not necessary in the vast majority of individuals. Approximately 90% to 95% of patients with a reported penicillin allergy can tolerate a rechallenge after an appropriate allergy evaluation has been performed.[8,9] The discrepancy between reported and actual penicillin allergy may be explained by the waning of penicillin IgE antibodies over time or by the misclassification of an adverse reaction or infectious manifestation as a drug reaction.[10-12] Sensitization to penicillin has been reported to decrease every 10 years, and after 20 years fewer than 1% of patients with initial clinical symptoms compatible with an allergic reaction continue to maintain their sensitivity. Therefore, a formal allergy evaluation is recommended by both North American and European guidelines to optimize patient management.[13-15]

Major symptoms of hypersensitivity. Hypersensitivity reactions to penicillin are classifiable as immediate or nonimmediate according to their clinical manifestation, time since the last drug administration, and the onset of symptoms.[16,17] Immediate reactions are predominantly IgE-mediated. They can occur within 6 hours after the last drug administration but typically occur within 1 hour of the first dose of a new treatment course.[17,18] Symptoms of an acute hypersensitivity reaction include urticaria, angioedema, conjunctivitis, respiratory symptoms (rhinitis, bronchospasm, cough, dyspnea), gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain), and/or anaphylaxis.[16]

Nonimmediate reactions occur more than 1 hour after the initial drug exposure, and they often develop days to weeks after medication initiation. Manifestations of nonimmediate reactions include maculopapular or morbilliform exanthems, particularly during treatment with amoxicillin or ampicillin. In addition, penicillins can elicit delayed urticaria/angioedema, exfoliative dermatitis, acute generalized exanthematous pustulosis (AGEP), and more severe bullous exanthems such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Furthermore, hematologic alterations may occur with certain penicillins, such as methicillin and ampicillin, and can cause interstitial nephritis, pneumonitis, hepatitis, and/or vasculitis with or without signs of serum sickness including joint involvement. The combination of skin eruptions, visceral involvement, hematologic alteration, fever, and lymphadenopathy is termed drug-induced hypersensitivity syndrome or drug rash (or reaction) with eosinophilia and systemic symptoms (DRESS). The pathogenic mechanisms involved in nonimmediate reactions are heterogeneous. Allergic maculopapular exanthems are T-cell—mediated diseases, in which drug-specific cytotoxic CD4 T cells migrate into the skin. These T cells then produce IL-5 and kill keratinocytes that present MHC class II molecules in a perforin-dependent manner.[19,20]

Diagnosis. Based on the clinical history and presenting symptoms, there are distinct diagnostic approaches for an immediate reaction and for a nonimmediate reaction to penicillin.

For patients with a history of TEN, SJS, DRESS, interstitial nephritis, or hemolytic anemia, reexposure through either drug challenge or desensitization is contraindicated, unless there are special circumstances.

Immediate reactions. Penicillins contain a core bicyclic structure that is composed of a 4-member β-lactam ring and a 5-member thiazolidine ring along with 1 side chain (R1) (Figure 1). Although too small to be antigenic in its native state, penicillin gains immunogenicity by spontaneously degrading and covalently binding to tissue or serum proteins to form haptens.[21] Approximately 95% of penicillin degrades to form a penicilloyl complex, which is called the major determinant.[21,22] The remaining penicillin remains in its native form (benzylpenicillin) or degrades further to form minor determinants, which include benzylpenicilloate and benzylpenilloate.

For an immediate reaction to penicillin or another β-lactam antibiotic, an IgE antibody to the common β-lactam ring as well as to a possible side chain must be assessed. A drug challenge test is the criterion standard for evaluating an IgE-mediated allergy both to penicillin and to other β-lactams. Skin testing and *in*

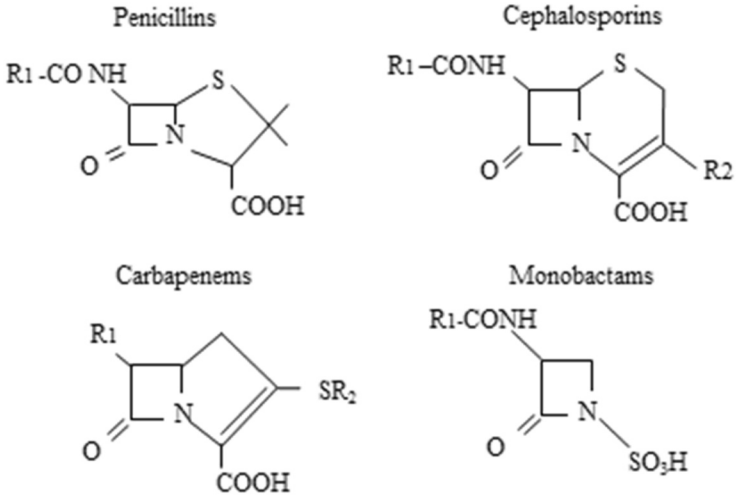

FIGURE 1. Basic chemical structures of β-lactams. R represents side chains that distinguish a β-lactam from other members of the same class of antibiotics.

vitro testing have been developed to identify a sensitization to a major/minor determinant and/or side chain and decrease the risk for a positive drug challenge test result.

Penicillin skin testing. For patients with a history concerning for an IgE-mediated reaction to penicillin, or whose past history is unclear, American and European guidelines recommend skin testing with both major penicillin antigenic determinants (penicilloyl-polylysine [PPL]) and minor antigenic determinants (benzylpenicillin [penicillin G], benzylpenicilloate, and benzylpenilloate).[13,15,23] In the United States, penicillin G is the only commercially available minor determinant, and it is used in combination with PPL (PRE-PEN; AllerQuest LLC, West Hartford, Conn), whereas in Europe, benzylpenicilloyl-octa-L-lysine and sodium benzylpenilloate (DAP; Diater, Madrid, Spain) are available as major and minor determinant, respectively.[8]

It has been estimated that skin testing with PPL and penicillin G, without the use of penilloate and penicilloate, may miss 10% to 20% of penicillin-sensitized subjects.[8,9,24-30] The clinical utility of penilloate and penicilloate is controversial because studies from North America have found a comparable negative predictive value (>95%) between skin testing to PPL and penicillin G only versus PPL and minor determinant mixture reagent in patients challenged to penicillin. Skin testing with penicillin G alone without the use of PPL is not recommended, because up to 70% of patients who have a positive skin test result react only to PPL, and these patients can still have a severe reaction.[24]

Furthermore, the patient populations who have undergone skin testing with PPL and penicillin G alone are not comparable to the ones who had all the reagents used for testing. Hence, it is not possible to compare the negative predictive value. In addition, recent or severe historical reactors are not typically included when only PPL and penicillin G are used for skin testing.

Epicutaneous and intradermal skin testing to PPL is performed using the commercially available undiluted concentration of 6×10^{-5} mol/L. A final epicutaneous and intradermal concentration used for penicillin G ranges between 5,940 and 10,000 U/mL and between 0.01 and 0.02 M for the other minor determinants (penicilloate and penilloate).[8,13] It is recommended that dilutions use saline, rather than sterile water, to lessen the possibility of false-positive reactions. A 1:10 or 1:100 dilution of PPL and minor determinants may be used selectively in patients who have experienced extremely severe reactions. In most guidelines, a positive result is a wheal having its greatest diameter at least 3 mm larger than that seen with negative control, though some authors suggest a 5-mm wheal for increased sensitivity, especially for PPL, for which a 5-mm wheal for prick puncture testing is recommended in the package insert.[8,13-15,31] Concentrations for penicillin skin testing are presented in Table I.

Pediatric patients and pregnant women who have experienced immediate reactions should be evaluated using the diagnostic protocol discussed earlier. Several studies have confirmed the safety of skin tests in children, with a rate of 1% to 3% of patients experiencing systemic reactions to skin testing.[32-34] The negative predictive value of an allergy evaluation that includes skin tests and drug challenge tests has been shown to be higher than 97% in children.[34,35]

Skin testing was also found to be safe in 56 pregnant women with group B *Streptococcus* colonization, with only 2 (4%) women experiencing a mild reaction during skin testing.[36] An oral challenge was not performed at the time of the skin testing, but of the skin test−negative women, 47 (89%) went on to receive a full therapeutic dose of a penicillin-class antibiotic during the peripartum period with no systemic reactions observed.

In vitro tests. Serum-specific IgE assays offer the most common *in vitro* method for evaluating immediate reactions to penicillins in both Europe and the United States. The most widely used commercial method is the fluoroimmunoassay (ImmunoCAP;

TABLE I. Concentrations for penicillin skin testing

Reagent	Epicutaneous	Intradermal
Penicilloyl-polylysine (PRE-PEN)	6×10^{-5} M	6×10^{-5} M
Penicillin G	10,000 units/mL	100 units/mL* 1,000 units/mL* 10,000 units/mL
Penicilloate	0.01-0.02 M	0.01-0.02 M
Penilloate	0.01-0.02 M	0.01-0.02 M

M, mole.
*Optional, based on physician discretion.

Thermo-Fisher, Uppsala, Sweden), which is available for a limited number of penicillins: penicillin G, penicillin V, amoxicillin, and ampicillin. The low sensitivity (0%-50%) has limited its use in the United States and seems to correlate with the severity of the reaction.[37-40]

Basophil activation test (BAT) has also been evaluated as a diagnostic tool for immediate hypersensitivity reactions to penicillin and other β-lactams. Its sensitivity is approximately 50%, with a specificity of more than 90%.[39,41] This test has not been validated, is not commercially available, and is not recommended for clinical use at this time.

Drug challenge tests. The negative predictive value for penicillin skin testing has been shown to be greater than 95% in North American studies. A small subpopulation of patients remains at risk for a potentially severe hypersensitivity reaction when rechallenged to penicillin.[8,28]

Drug challenge is the diagnostic criterion standard for the exclusion of an immediate reaction and is recommended after allergy evaluation when the patient is deemed unlikely to be allergic to the given drug.

After negative penicillin skin test result, amoxicillin is typically administered as a drug challenge often as a single full dose and occasionally as 1/10th of the final dose and then the final dose. Amoxicillin is the penicillin most commonly used for drug challenges because it has both immunologically significant core penicillin structures and potentially significant R-group side chains.[42] Challenge with the drug that caused the reaction, such as amoxicillin-clavulanate, may also be considered.

Retesting. Resensitization is an uncommon occurrence that develops in upto 2% of patients after re-treatment with a penicillin.[43-45] The use of parenteral antibiotics may increase the risk.[46] Both North American and European guidelines suggest that repeat skin testing may be considered for patients with severe immediate reactions, especially after parenteral administration, even when a therapeutic course of penicillin has previously been tolerated.[13-15] However, most patients with a history of penicillin allergy who have undergone negative skin testing and challenge may receive future courses of penicilllins without a significantly increased risk of reactions, compared with the general population. A recent retrospective study of 32 patients indicated that in patients who report penicillin allergy and have negative penicillin skin testing result, repeated administration of intravenous penicillin antibiotics appears safe.[47]

Nonimmediate reactions. Both delayed reading of intradermal tests (IDTs) and patch tests have been described as diagnostic tools for nonimmediate reactions. These tests have not yet been standardized or validated. In the United States, patch testing and delayed reading of IDTs are not yet routinely performed, but they are included in European guidelines.[15]

Delayed-reading IDTs. IDT is performed using penicillin G as well as any other suspect penicillins or β-lactams. Delayed skin testing with PPL and other minor determinants has been found to have limited diagnostic value.[48]

Penicillin G is administered at a concentration of 10,000 U/mL, whereas a concentration of 1 to 20 mg/mL can be used for other suspect penicillins (eg, ampicillin and amoxicillin).[48] The clinician should start with epicutaneous prick testing. If results are negative after 15 to 20 minutes have elapsed, one should proceed next to IDT. Again, results are read after 20 minutes to assess any immediate responses. Additional readings of delayed reaction to skin tests are performed after 48 and 72 hours. Any infiltrated erythema with a diameter larger than 5 mm is considered to be a positive reaction.

Patch test. A patch test for penicillin and other suspect penicillins/β-lactams is performed using a concentration of 5% to 10% penicillin in petrolatum. The patch should be worn for 48 hours, with readings 15 minutes after removal of the strips and again 24 hours later.

The specificity for both delayed reading of IDTs and patch testing is high (90%-100%), but the sensitivity is less than 50% to 60%.[20,49] Delayed-reading IDTs appear to be more sensitive than patch testing but may also be less specific.[50,51] Repeat exposure to the drug is often avoided, but there is limited data on the utility of using these 2 procedures to assist in the evaluation of non−IgE-mediated drug reactions.[49,52,53] A recent consensus document indicated that patch testing and delayed intradermal readings could be of use for the diagnosis of maculopapular rashes, AGEP, and DRESS. Although patch testing may be considered in SJS and TEN, delayed reading of IDT is contraindicated in these 2 conditions.[54] A multicenter study evaluated 134 patients with severe cutaneous reactions to drugs: 72 with DRESS, 45 with AGEP, and 17 with SJS⁄TEN.[52] Patch tests were first performed with drugs diluted to 1%, and if the results were negative, they were repeated with the drug diluted to 30% in petrolatum. Seventy-six participants (56.7%) had positive patch-test results: 46 (64%) of the 72 with DRESS (of the antibiotics, 8 were positive to amoxicillin, 1 to dicloxacillin, 2 to ceftriaxone, and 1 to imipenem), 26 (58%) of the 45 with AGEP (7 were positive to amoxicillin and 1 to ceftriaxone), and 4 (24%) of the 17 with SJS⁄TEN (1 was sensitive to amoxicillin). In patients with negative patch-test results, 4 of 11 patients with AGEP and 3 of 4 patients with DRESS associated with β-lactams were positive on delayed-reading IDTs.

Drug challenge test. A drug challenge test may be considered for some nonimmediate reactions. Multiple protocols have been published for such drug challenge tests.[14,15] A full therapeutic dose can be administered on the first day or can be given incrementally over days to weeks. Some studies suggest that an additional treatment course for 7 to 10 days after the full therapeutic dose is needed to sufficiently exclude a nonimmediate reaction.[55,56] A potential caveat of this approach lies in exposing patients with a history of benign reactions to an unnecessary therapeutic course of penicillin.

Other penicillins

Aminopenicillins. Amoxicillin and ampicillin are 2 of the most commonly prescribed aminopenicillins. Immediate reactions are IgE-mediated to either the common β-lactam structure or the R-group side chain.[57] Patients who are suspected or found to have a sensitization to amoxicillin or ampicillin should avoid drugs with similar or identical R-group side chains (until a formal allergy evaluation can be performed). These drugs include cefadroxil, cefprozil, and cefatrizine (identical side chain shared with amoxicillin and similar for ampicillin) as well as cephalexin, cefaclor, cephradine, cephaloglycin, and loracarbef (similar for amoxicillin and identical for ampicillin).[13,14] The avoidance of cephalosporins with identical/similar side chains does not hold true if the patient has already tolerated 1 of them, even if he or she is still avoiding penicillins.

Studies have suggested that amoxicillin sensitivity is more prevalent among European patients, with up to 50% of patients with a history of penicillin allergy determined to be sensitized to

TABLE II. Nonirritating concentrations for penicillin and β-lactams

Penicillin	Nonirritating concentration
Penicillin G[14,79]	10,000 units/mL
Aminopenicillins	
Amoxicillin[14,21,79]	3-25 mg/mL
Ampicillin[14,21,79]	2.5-25 mg/mL
β-Lactamase—resistant	
Nafcillin[80]	25 μg/mL
Carboxypenicillins	
Ticarcillin[80]	20 mg/mL
Ureidopenicillins	
Piperacillin[928]	20 mg/mL
Carbapenems	
Meropenem[64]	1 mg/mL
Imipenm[61,63]	0.5-1 mg/mL
Ertapenem[61]	1 mg/mL
Monobactam	
Aztreonam[61]	2 mg/mL

TABLE III. Oral penicillin desensitization protocol*[70]

Step	Penicillin V (units/mL)	mL	Units	Cumulative dose (units)
1	1,000	0.1	100	100
2	1,000	0.2	200	300
3	1,000	0.4	400	700
4	1,000	0.8	800	1,500
5	1,000	1.6	1,600	3,100
6	1,000	3.2	3,200	6,300
7	1,000	6.4	6,400	12,700
8	10,000	1.2	12,000	24,700
9	10,000	2.4	24,000	48,700
10	10,000	4.8	48,000	96,700
11	80,000	1.0	80,000	176,700
12	80,000	2.0	160,000	336,700
13	80,000	4.0	320,000	656,700
14	80,000	8.0	640,000	1,296,700

*Fifteen-minute intervals between each step. Cumulative dose is 1.3 million units given over a total of 3h 45 min.

amoxicillin only, compared with 0% to 6% in North America.[8,26,58] As a result, European guidelines recommend that amoxicillin skin testing be performed concurrently with penicillin for all patients, whereas testing for amoxicillin is not consistently performed in North America.[14,15]

Unlike skin testing for penicillin, skin testing for amoxicillin and ampicillin is not validated, and the predictive value is unknown. A drug challenge test is required to assess for an immediate reaction. Skin testing can be performed using nonirritating concentrations that can potentially help identify sensitized individuals. Nonirritating concentrations of amoxicillin range from 3 to 25 mg/mL. Similar to penicillin-specific IgE, amoxicillin-specific IgE diminishes over time. One study found that all 24 patients who were found to be skin test positive after exposure to the drug were skin test negative after 5 years.[10] Because the parenteral form of amoxicillin is not available in the United States, equivalent concentrations for skin testing cannot be reliably achieved. For ampicillin, skin testing is performed using a concentration of 2.5 to 25 mg/mL. Recently, the Food and Drug Administration (FDA) is evaluating a Penicillin Kit that will contain amoxicillin.[30]

If skin testing result is negative, a drug challenge test is recommended. If either skin testing result or the oral challenge is positive, then avoidance or desensitization is recommended.

Carbapenems. Carbapenems (imipenem/cilastatin, meropenem, ertapenem) share a common β-lactam ring, giving rise to concern for possible cross-reactivity (Figure 1). Studies over the last decade, performed either on adults or on children, have demonstrated an absence or very low (1%) rate of cross-reactivity between penicillins and carbapenems.[59-65] Nonirritating concentrations for skin testing to common carbapenems are listed in Table II.

For patients with a history of an immediate reaction and negative skin testing result to penicillin, carbapenem should prove safe. If penicillin skin testing is not available or cannot be performed, then a carbapenem drug challenge test is recommended. For a positive penicillin skin test result, carbapenem can be administered as a 2-step graded challenge.[61] If skin testing result is negative, it is reasonable to administer a single full-dose challenge.[61]

Monobactams. Monobactams consist of a monocyclic β-lactam ring structure with no adjoining rings (Figure 1). Currently, the only commercially available monobactam is aztreonam. Studies have demonstrated a lack of cross-reactivity between penicillin and aztreonam.[61,66,67] A lack of cross-reactivity has also been demonstrated between cephalosporins and aztreonam, with the exception of ceftazidime, which shares an identical side chain.[66] Skin testing is performed with a nonirritating concentration of 2 mg/mL. Aztreonam may be given to patients with a history of penicillin allergy.

Clavulanate. Clavulanate is a β-lactam inhibitor and is frequently combined with a penicillin such as amoxicillin. Although uncommon, clavulanate has been reported as a causative agent for immediate hypersensitivity reactions. Skin testing with an epicutaneous concentration of clavulanate at 10 mg/mL and intradermal concentrations of 0.1 and 1 mg/mL was found to be nonirritating in 1 small case series.[68] Skin testing with intravenous solutions of amoxicillin-clavulate has also been reported.[69] Given the limited availability of isolated clavulanate/clavulanic acid and intravenous amoxicillin/clavulanic acid in the United States, a drug challenge to amoxicillin/clavulanic is recommended if clavulanate is suspected and the initial drug challenge to amoxicillin is negative.

Management

High-risk patients. Individuals with a demonstrated sensitivity to penicillin, either on positive skin testing or on failed drug challenge tests, should avoid the responsible drug as well as those that are potentially cross-reactive. It is reasonable to repeat skin testing if many years have passed since previous skin testing. If there are no reasonable alternatives, both oral and intravenous desensitization protocols have been well established in American and European guidelines.[13,15] Examples of these are provided in Tables III and IV, respectively.[70,71]

Low-risk patients. For patients who are at low risk of an immediate hypersensitivity reaction, including those with a history of itching without urticaria, mild maculopapular rash (ie, less than 1-week duration), or other benign rash, a drug challenge test may be considered without the use of skin testing.[72] Tools, such as a recently published clinical pathway for patients with penicillin allergy, can help guide physicians in deciding whether

TABLE IV. Example of intravenous desensitization protocol for β-lactam dose of 1 g*[13]

Solution	Volume of diluent (mL)	Drug concentration (mg/mL)	Total drug to be injected into each bottle (mg)
Solution 1	250	0.04	10
Solution 2	250	0.4	100
Solution 3	250	4	1000

Step	Solution	Rate (mL/h)	Time (min)	Administered dose (mg)	Cumulative dose (mg)
1	1	2	15	0.02	0.02
2	1	5	15	0.05	0.07
3	1	10	15	0.1	0.17
4	1	20	15	0.2	0.37
5	2	5	15	0.5	0.87
6	2	10	15	1	1.87
7	2	20	15	2	3.87
8	2	40	15	4	7.87
9	3	10	15	10	17.87
10	3	20	15	20	37.87
11	3	40	15	40	77.87
12	3	80	172.9	922.13	1000
Total infusion time			337.9 min		

*Modified with permission from Castells.[71]

drug challenge, drug sensitization, drug avoidance, or further allergy evaluation presents the best course of action.[73]

Cephalosporins (by Kimberly Blumenthal, MD)

General. Cephalosporin adverse drug reactions (ADRs) affect about 0.5% to 2.5% of patients. ADRs include nephropathy and acquisition of *C difficile* colitis.[74] Although cephalosporin allergy is approximately 10-fold less common than penicillin allergy, it remains one of the most commonly reported drug allergies in the United States.[75]

Major symptoms. Cephalosporins can elicit various hypersensitivity reactions, including IgE-mediated reactions characterized by urticaria, angioedema, rhinitis, bronchospasm, and anaphylaxis. Notably, cephalosporins, especially cefaclor and cefprozil, may cause serum sickness–like reactions.[13] They may also less frequently lead to severe cutaneous adverse reactions (SCARs) and isolated eosinophilia.[74,76]

Diagnosis

Immediate hypersensitivity skin testing. Most hypersensitivity reactions to cephalosporins are directed at the R-group side chain (Figure 2) rather than the core β-lactam ring molecule.[77,78] However, it may be useful to also perform penicillin skin testing when patients present with possible sensitivity to cephalosporins, particularly those in the earlier generations, which include the aminocephalosporins (cefaclor, cephalexin, and cefadroxil; Table V). Although skin testing to native cephalosporins is not standardized, a positive skin test result with a nonirritating concentration suggests the presence of drug-specific IgE antibodies.[79,80] A negative skin test result does not rule out an allergy, and must be followed by an observed graded challenge (Table VI). Similar to data suggestive of loss of IgE-mediated hypersensitivity to penicillins, patients with IgE-mediated allergy to cephalosporins may lose sensitivity over time.[81]

Delayed hypersensitivity skin testing. For SCARs, using the RegiSCAR scoring method for diagnosis is recommended, and skin biopsy is usually indicated.[82] Patch testing may be useful, especially for DRESS syndrome and AGEP.[77] Patch tests to cephalosporins may be performed using a 30% dilution of the drug in petrolatum (not commercially available in the United States), with readings at 48 and 72 hours.[52]

Management

General/clinical pathways. For patients with true or reported cephalosporin allergy, management can be challenging, especially for nonallergist providers. A clinical pathway that incorporates both cephalosporin generation (because of β-lactam ring relevance by generation) and cephalosporin side chain (because of cross-reactivity by side chain/R group) can help direct safe use of β-lactam in the setting of previously reported hypersensitivity, though outcome data are limited (Figure 3, *A*).[73] Similar pathways have been implemented for demonstration of cephalosporin tolerance in patients with historical penicillin allergies (Figure 3, *B*).[73] To date, data on these clinical pathways confirm that they increase β-lactam use in acute therapeutic situations and increase first-line antibiotic treatment in an appropriately risk-adverse manner (reactions were observed in 0.5%-4.0% of patients).[73,83]

Oral challenge. An oral challenge to cephalosporin would be appropriate if the reaction appeared to be (1) unlikely to have been caused by the cephalosporin, (2) not immune-mediated/serious/life-threatening, or (3) in response to a different cephalosporin with low to medium risk of cross-reactivity (eg, cephalosporins with dissimilar side chain, history of IgE-mediated penicillin allergy). As with any other drug challenge, the potential risks, benefits, and alternatives should be discussed with the patient and/or the patient's parents/guardians and informed consent should be obtained. The procedure should be performed in a monitored clinical setting where emergency support is readily available. Generally, drug challenges to dissimilar cephalosporins are safe to perform.

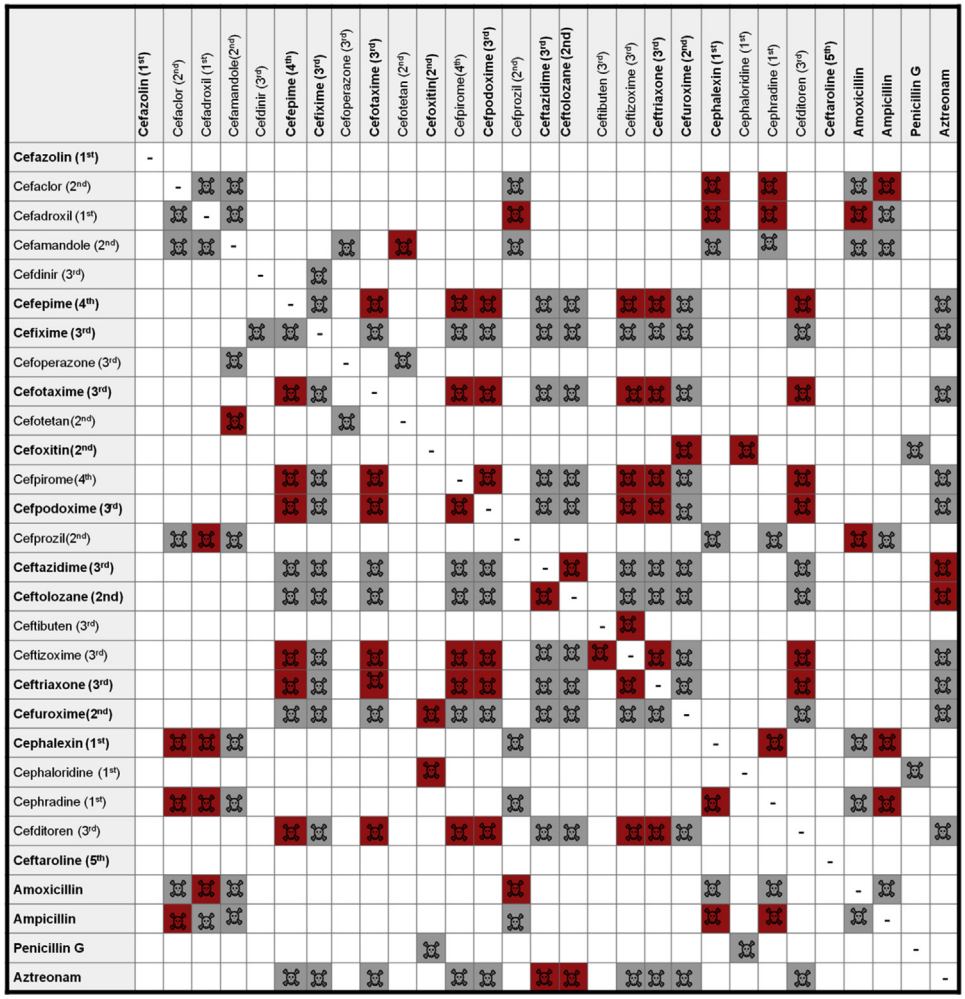

FIGURE 2. Cephalosporin cross-reactivity.[78] β-Lactam antibiotics can have similar or identical R1 or R2 side chains, which may make cross-reactivity more likely. This matrix indicates either a similar (gray) or an identical (red) side chain. Empty boxes indicate a lack of side-chain similarity.

TABLE V. Immediate hypersensitivity cephalosporin skin testing[80,929-931]

Test type	Cephalexin	Cefazolin	Cefuroxime	Cefotaxime	Ceftazidime	Ceftriaxone	Cefepime*	Cefixime
Step 1: Epicutaneous	25 mg/mL	330 mg/mL	100 mg/mL	100 mg/mL	100 mg/mL	100 mg/mL	200 mg/mL	2 mg/mL
Step 2: Intradermal†	NA‡	3.3 mg/mL	1 mg/mL	1 mg/mL	1 mg/mL	1 mg/mL	2 mg/mL	NA‡
Step 3: Intradermal	NA‡	33 mg/mL	10 mg/mL	10 mg/mL	10 mg/mL	10 mg/mL	20 mg/mL	NA‡

NA, Non-applicable/not available.
Penicillin skin testing may also be appropriate for patients presenting with cephalosporin allergy.
*Nonirritating in clinical practice, MGH Allergy Associates (unpublished data, 2020).
†Optional for patients with history of severe and/or recurrent reactions.
‡Cephalexin and cefixime are not available as an intravenous preparation.

Increased caution, warranting skin testing–guided treatment, choosing alternative agents, or performing a desensitization, may be indicated for cephalosporin administration with similar side chains, or for patients with severe reaction histories, or clinically unstable patients. In cases of serum sickness–like reaction to cefaclor or cefprozil, it is appropriate to use another cephalosporin, preferably one with dissimilar R1 side chains. A standard 2-step test dose protocol is as safe as longer protocols, but less likely to induce tolerance (Table IV).[83,84]

Desensitization. The most common desensitization protocol for cephalosporins comprises 12 steps and it is intended for IgE-mediated reactions (Table IV).[13] Contraindications to desensitization include severe T-cell–mediated reactions such as DRESS, TEN, or SJS. Although initiating treatment with standard desensitization protocol is recommended, its duration may be modified in such a manner that it takes into account a patient's relevant history and considers both comorbidities and acuity of the present illness.

TABLE VI. Cephalosporin drug challenge[73,84]

Step 1	1/4 of an oral dose/pill/1/10th of parenteral or oral liquid dose, observe for 30-60 min
Step 2	1 full dose, observe for 60 min

Sulfamethoxazole-trimethoprim (by Miguel Park, MD)

Epidemiology. Sulfamethoxazole-trimethoprim (SMZ-TMP) is a common cause of hypersensitivity and ADRs. Before 1982, SMZ-TMP was the second most common medication behind amoxicillin to result in cutaneous ADRs in the hospital.[85] These reactions are primarily due to hypersensitivity to the sulfonamide component, and specific hypersensitivity to trimethoprim is rare and has been reported anecdotally.[86] Patients with HIV have been reported to have a rate of sensitivity to SMZ-TMP that ranges from 34% to 50%[87,88]; however, the frequency of cutaneous ADRs exceeds that of those that occur in response to aminopenicillins.[89]

Most ADRs to SMZ-TMP are morbilliform, maculopapular eruptions. IgE-mediated reactions including urticaria/angioedema and anaphylaxis, severe delayed hypersensitivity reactions (DHRs) such as SJS, TEN, and DRESS, and hepatic, renal, and hematologic reactions have also been described.[13]

Diagnosis. Validated diagnostic testing is not currently available for SMZ-TMP hypersensitivity.[90] However, if an IgE-mediated ADR to SMZ-TMP is suspected, skin testing using a nonirritating concentration of 1:100 dilution of 80 mg/mL, or 0.8 mg/mL, may be considered.[80] A positive result could suggest IgE-mediated sensitization, and a negative result would not rule out an IgE-mediated reaction to SMZ-TMP. Oral challenge, either as a single full dose or as 1/10th of the dose followed by the full dose, may be considered on the basis of clinical history and skin test results.[91] Dapsone may be tolerated in patients with histories of sulfonamide reactions; however, there is conflicting information on cross-reactivity, and avoidance of dapsone is recommended in patients with histories of severe reactions to sulfonamides.[92]

Management. Desensitization is an important component in the management of SMZ-TMP hypersensitivity. The term *desensitization* has traditionally been used for IgE-mediated sensitivity. It has also been applied to treatments for reactions to SMZ-TMP, even when the mechanisms underlying the reaction are unclear. The Joint Task Force on Practice Parameters has recommended that the term "temporary induction of tolerance"[13] is more appropriate than desensitization in these circumstances.

In the event of severe DHRs (SJS, TEN, DRESS, and others) to SMZ-TMP, the drug should be avoided. If no alternatives exist and the benefits of treatment with SMZ-TMP outweigh the risk of death from a severe hypersensitivity reaction,[13] a previously reported temporary induction of tolerance protocol that was successfully used for 2 patients may be considered.[93]

Most literature on the temporary induction of tolerance to SMZ-TMP focuses on the HIV patient population. The various protocols for temporary induction of tolerance to SMZ-TMP have shown similar success rates (initial success: 80%-90%; long-term: 60%-80%) (Table VII).[89,94-104] There is no current consensus on the best protocol for SMZ-TMP temporary induction of tolerance. Interestingly, when patients with a history of mild to moderate SMZ-TMP hypersensitivity were randomized to temporary induction of tolerance or full-dose challenge, they showed similar success rates in tolerating the drug (Table VIII). Some studies found full-dose challenge success rates to range from 58% to 72% and those of temporary induction of tolerance to range from 60% to 80%.[94,97,102] Leoung et al[98] reported a 75% success rate in the temporary induction of tolerance group compared with 58% in the full-dose challenge group (58%) ($P = .014$). Therefore, a full-dose challenge could be considered for patients with mild reactions to SMZ-TMP as an alternative to an induction of tolerance procedure.

Very few studies have examined the temporary induction of tolerance to SMZ-TMP in non-HIV patient populations.[99,105] Mann et al[99] described 4 patients with a history of SMZ-TMP hypersensitivity (leukopenia, hives, macular rash, morbilliform rash) who underwent a successful temporary induction of tolerance using either an 8-day protocol or a 22-day protocol.[106,107] Pyle et al[108] reported that 90% of 72 patients with a history of SMZ-TMP hypersensitivity who required the drug and underwent temporary induction of tolerance had successful outcomes with the 6-step, 14-step, or more than 1-day protocols. The data suggest that SMZ-TMP temporary induction of tolerance may be considered in non-HIV patients with a history of related hypersensitivity. The procedure appears to result in success rates comparable to those seen in patients with HIV.

In summary, temporary induction of tolerance to SMZ-TMP can be used safely and effectively in patients with and without HIV who have SMZ-TMP hypersensitivity. For HIV-positive patients with a history of a mild SMZ-TMP hypersensitivity, a full-dose challenge can be considered; however, this option may result in higher rates of ADRs than those associated with the temporary induction of tolerance. A standardized temporary induction of tolerance protocol for SMZ-TMP is not currently available, and a range of temporary induction of tolerance protocols may be appropriate for use with HIV-positive patients (Table VII). Tables IX, X, and XI present protocols described by Pyle et al,[108] which offer options for temporary induction of tolerance to SMZ-TMP for non-HIV patients.

Quinolones (by Maria Jose Torres, MD)

Introduction. The frequency of hypersensitivity reactions to quinolones, especially anaphylactic reactions, is increasing, likely related to the increase in their use. They can induce IgE- and T–cell–dependent reactions, with the IgE type being the most common, and moxifloxacin as an increasing inductor of reactions.[109-112] Factors influencing the increase in moxifloxacin IgE hypersensitivity in countries where it is prescribed are not known.[109-111] A mast cell–specific receptor has been identified (MRGPRX2), which is a target for direct activation by quinolones and some other drugs with tetrahydroisoquinoline (THIQ) motifs.[113] A previous diagnosis of immediate hypersensitivity to β-lactams can be a risk factor for developing IgE reactions to quinolones.[110] Ciprofloxacin is the main quinolone involved in delayed reactions.[112]

Clinical symptoms. The most frequent clinical symptoms are immediate urticaria and anaphylaxis, with some reports indicating that they can be severe.[109-112] Delayed reactions usually reported are maculopapular exanthem, delayed urticaria, and fixed drug eruptions. Although less frequent, other reactions such as AGEP, SJS, and TEN have also been described.

Diagnosis. Various factors can complicate the diagnosis of immediate hypersensitivity reactions to quinolones. First, the clinical history is often unreliable, because nearly 70% of patients with a clinical history of quinolone hypersensitivity ultimately

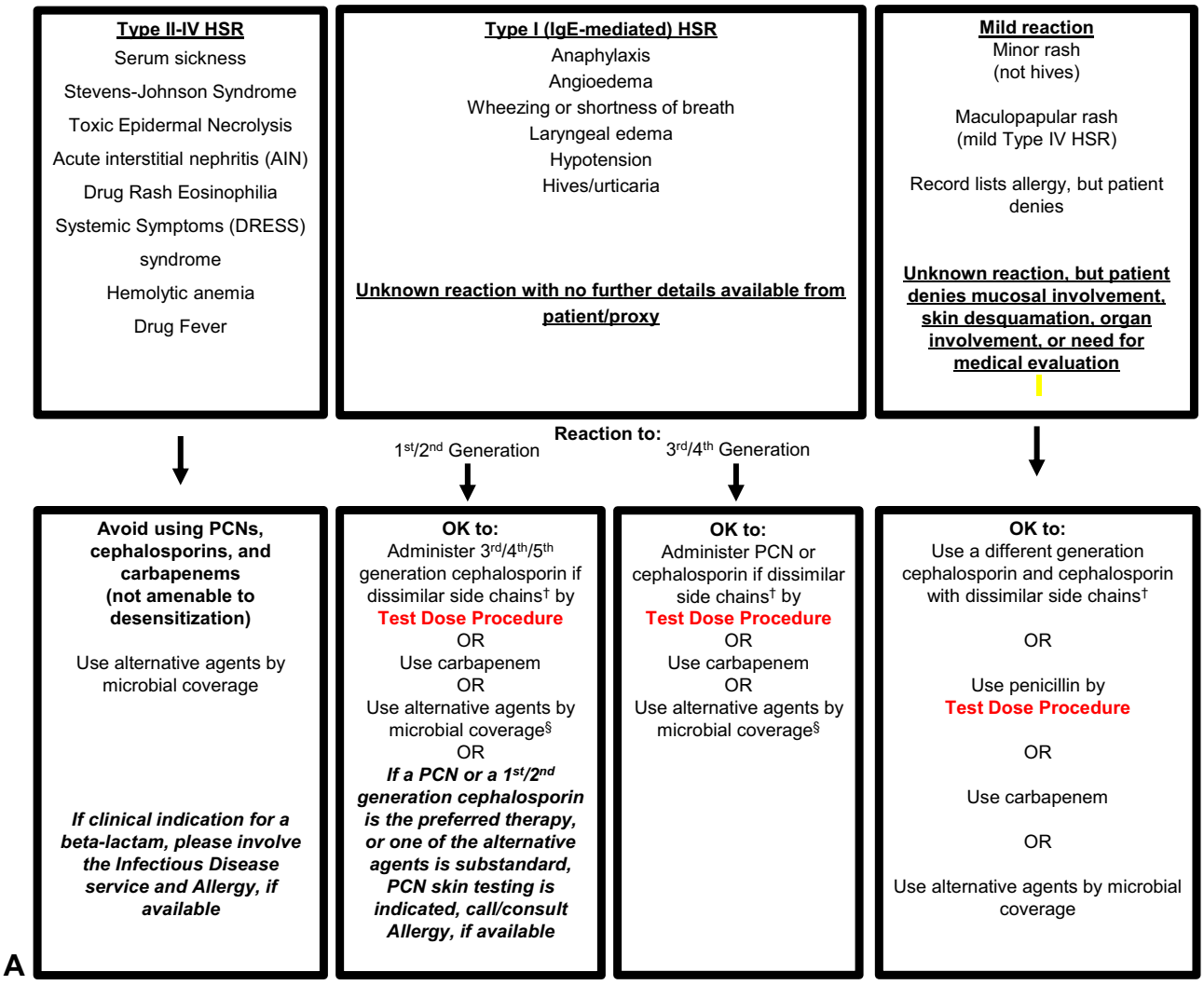

FIGURE 3. Cephalosporin hypersensitivity pathway[73] in patients with a history of reported hypersensitivity to (**A**) cephalosporins and (**B**) penicillin. *PCN,* Penicillin class antibiotic.

can tolerate the drug and are therefore not allergic.[110,112] Second, skin testing has resulted in a high number of false-positive results, likely due to the capacity of some quinolones to induce direct histamine release.[109,110,112,114] Table XII summarizes quinolone concentrations most frequently recommended in the current literature.[112,114,115] Therefore, drug challenge is the most useful diagnostic assay, and procedure-related anaphylaxis is rare in properly selected patients. Table XIII presents the recommended procedures for drug challenge tests. Recently, *in vitro* approaches, such as radioimmunoassay and BAT, have proved useful tools for diagnosis, though their sensitivity is not optimal and they are not commercially available.[109,110,114]

The diagnosis of delayed reaction is also difficult, and particularly relevant is the lack of reliability of the clinical history, where fewer than 5% of cases evaluated are finally confirmed as allergic.[110,112] Patch testing has shown high specificity but low sensitivity. In cases with maculopapular exanthems or delayed urticaria, the most frequent clinical symptoms, the diagnosis is usually confirmed with a drug challenge test.

Management. Although there are no general rules for predicting cross-reactivity, this seems to exist between first- and second-generation quinolones, with lower levels seen with the third- and fourth-generation quinolones. Therefore, patients with immediate hypersensitivity to quinolones are recommended to avoid the administration of the whole group, and specific recommendations of tolerance need to be made on a patient-by-patient basis using a drug challenge test. For higher-risk patients, desensitization to quinolones may be considered (Table XIV). However, cross-reactivity in delayed reactions seems to be low.

Macrolides (by Miriam Verdu Benhamu, MD, Anca Mirela Chiriac, MD, and Pascal Demoly, MD, PhD)

General. Macrolide antibiotics are considered to be some of the safest antibiotic treatments available. Their chemical structure is characterized by a large lactone ring, which can vary from 12 to 16 atoms, with 1 or more sugar chains attached.[116] There are more than 20 macrolide antibiotics available; erythromycin

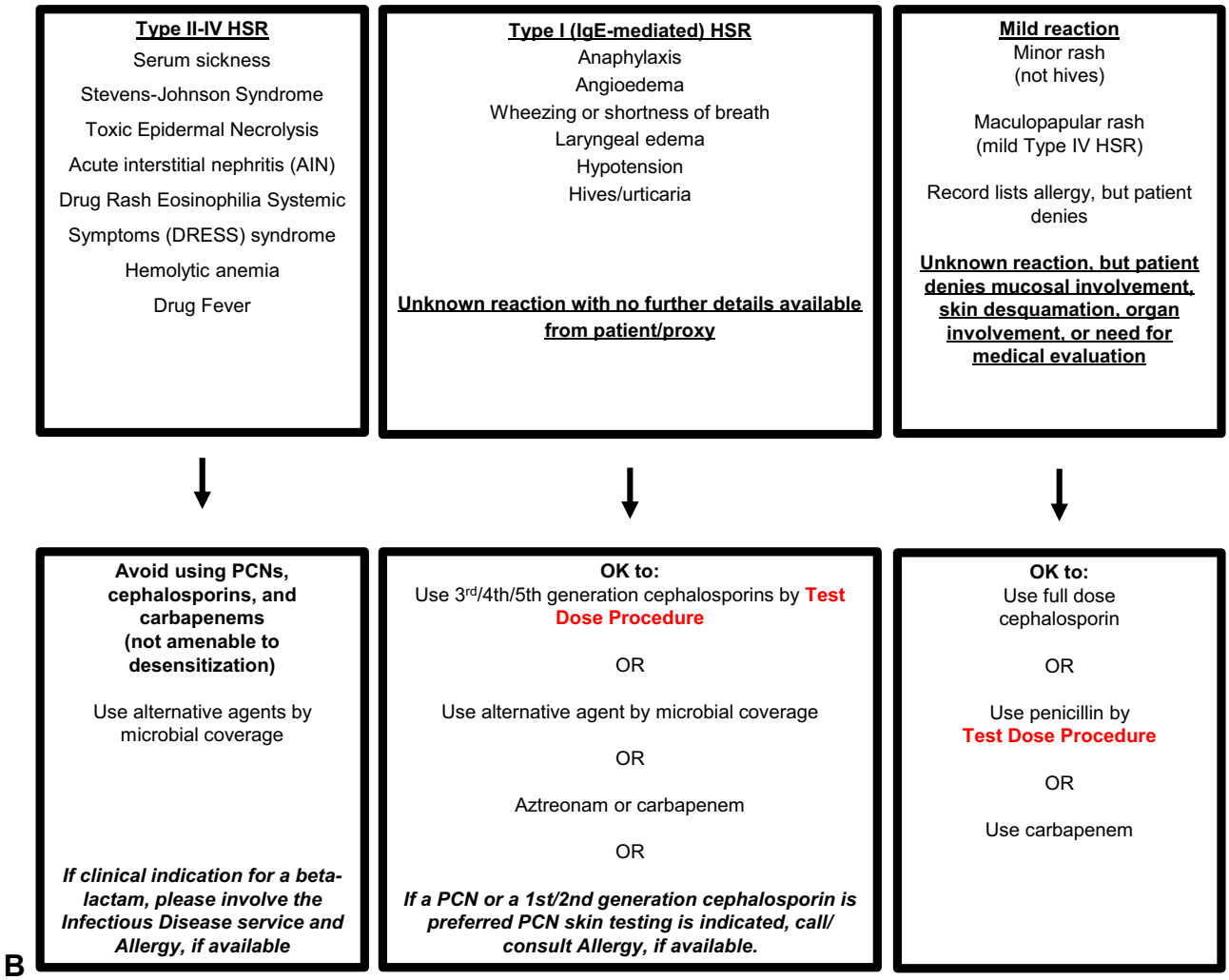

FIGURE 3. (*CONTINUED*).

TABLE VII. SMZ-TMP temporary induction of tolerance in patients with HIV

Study author/year	No. of subjects	Protocol		Success rate (%)	
		Starting dose	No. of steps/duration	Initial	Long- term*
Absar et al,[94] 1994	28	2 mg	10/10 d	82%	61%
Gluckstein and Ruskin,[96] 1995	22	0.02 mg	6/5 h	86%	71%
Nguyen et al,[100] 1995	45	10 ng	40/36 h	82%	60%
Kalanadhabhatta et al,[97] 1996	13	2 ng	37/27 h	100%	100%
Caumes et al,[95] 1997	48	4 mg	8/3 d	83%	77%
Rich et al,[101] 1997	22	20 ng	8/8 d	86%	86%
Ryan et al,[102] 1998	13	2 mg	33/33 d	69%	62%
Yoshizawa et al,[104] 2000	17	2 mg	10/5 d	88%†	88%
Bonfanti et al,[932] 2000	34	10 ng	40/36 h	79%	79%
Leoung et al,[98] 2001	97	50 mg	12/6 d	93.8%	75%
Straatmann et al,[103] 2002	9	75 mg	11/22 d	60%	60%

*Those who died unrelated to SMZ-TMP and lost to follow-up were counted as part of the successful group.
†Some patients required multiple tries before successful completion.

TABLE VIII. SMZ-TMP temporary induction of tolerance vs full-dose challenge

Study author/year	Success rate % (total no. of subjects in the group)	
	Temporary induction of tolerance	Full-dose challenge
Bonfanti et al,[931] 2000	79.5% (34)	72% (25)
Leoung et al,[98] 2001	75% (97)	58% (94)
Straatmann et al,[103] 2002	60% (9)	60% (9)

TABLE IX. SMZ-TMP temporary induction of tolerance short protocol*

Steps	Dose of SMZ-TMP
1	0.02 mg/0.004 mg
2	0.2 mg/0.04 mg
3	2 mg/0.4 mg
4	20 mg/4 mg
5	200 mg/40 mg
6	**Final dose** Single (SS): 400 mg/80 mg PO or Double (DS): 800 mg/160 mg PO

PO, *per os* (by mouth).
*Dosing intervals are scheduled 15, 30, or 60 min apart. Depending on the dosing interval, the test will take 2 h at 15-min intervals, $3^1/_2$ h at 30-min intervals, and $6^1/_2$ h at 60-min intervals. Modified from the temporary induction of tolerance protocol by Gluckstein and Ruskin.[96]

was the first macrolide used, and this molecule has 14 atoms in the lactone ring (14-C), such as clarithromycin and roxithromycin; azithromycin is the only macrolide with 15-C, and josamycin and spiramycin have 16-C. Macrolide antibiotics usually have a bacteriostatic effect by inhibiting the mRNA-direct protein synthesis after binding to the 50S ribosomal subunit; they are broad-spectrum antibiotics effective against gram-positive, gram-negative, and atypical pathogens. Their clinical uses include upper and lower respiratory tract infections, skin infections, sexually transmitted diseases, and the eradication regimen of *Helicobacter pylori*. Their pharmacokinetic properties include low to moderate oral bioavailability and extensive diffusion into tissues and fluids due to their lipophilic nature. The 14-membered ring macrolides have an affinity for cytochrome p450 (CYP450); therefore, potential drug interactions must be taken into account when other drugs metabolized by CYP450 enzymes (such as phenytoin, cyclosporine, theophylline, and carbamazepine) are coprescribed.

Major symptoms. Published hypersensitivity reactions to macrolides include both immediate (<1 hour after drug intake) and nonimmediate (delayed) reactions.[116-120] Urticaria and/or angioedema are the most commonly described symptoms, but maculopapular exanthems (some severe, evocative of DRESS), fixed drug eruptions, and bullous skin reactions are also seen. Anaphylaxis caused by macrolides has also rarely been described.

In addition to hypersensitivity reactions, macrolides can induce gastrointestinal side effects, such as nausea, vomiting, diarrhea, and abdominal cramps, because they stimulate gut contractility.[116] Macrolides can also cause sensorineural ototoxicity, which is usually transient, as well as prolongation of the QT interval.[116]

TABLE X. SMZ-TMP temporary induction of tolerance long protocol*

Steps	Dose of SMZ-TMP
1	0.08 mg/0.016 mg
2	0.16 mg/0.032 mg
3	0.32 mg/0.064 mg
4	0.64 mg/0.128 mg
5	1.28 mg/0.256 mg
6	2.5 mg/0.512 mg
7	5 mg/1 mg
8	10 mg/2 mg
9	20 mg /4 mg
10	40 mg/8 mg
11	80 mg/16 mg
12	160 mg/32 mg
13	320 mg/64 mg
14	440 mg/88 mg

*Dosing interval is 15 min apart. The test will take 4 to 5 h. Modified from the temporary induction of tolerance protocol by Kalanadhabhatta et al.[97]

TABLE XI. SMZ-TMP temporary induction of tolerance 10-d protocol*

Steps	Dose of SMZ-TMP
1	2 mg /0.4 mg
2	4 mg/0.8 mg
3	8 mg/1.6 mg
4	16 mg/3.2 mg
5	40 mg/8 mg
6	80 mg/16 mg
7	160 mg/32 mg
8	320 mg/64 mg
9	400 mg/80 mg
10	800 mg/160 mg

*Dosing interval is daily. The test will take 2 h on the first day and 90 min on subsequent days. Modified from the temporary induction of tolerance protocol by Absar et al.[94]

Diagnosis. When hypersensitivity to macrolides is suspected, the most common approach adopted by physicians is avoidance especially because these agents are rarely indicated as first-line treatment.[116,121] However, clinical history alone is insufficient to ascertain the diagnosis, and published series reveal that, after performing a drug challenge test, hypersensitivity to macrolides is confirmed in only 2.7% to 17% of cases.[118,120] Therefore, in some situations, including the prevention/treatment of *Toxoplasma gondii*, eradication of *H pylori*, and treatment of some atypical *Mycobacteria*, testing should be performed.

A detailed *clinical history* including the macrolide involved, the chronology, and type of reaction, as well as the treatment used, is always needed.

Skin tests (prick and sequenced IDT for immediate reactions with the few available injectable forms and delayed-reading IDTs and patch tests for nonimmediate reactions) can be helpful in the diagnostic evaluation. They are not fully validated, because it is necessary to perform them in a large number of patients with proper controls, and therefore, real predictive values are unknown. In a study by Empedrad et al,[80] concentrations for intradermal testing with erythromycin and azithromycin were tested in 25 healthy subjects

TABLE XII. Recommended concentrations of quinolones for skin testing*[80,112,115]

Quinolone	Concentration prick (mg/mL)	Concentration IDT (mg/mL)	References
Moxifloxacin	1.6	Not performed	Seitz et al,[112] 2009
	Tablet, 400 mg suspended in saline	Not performed	Venturini et al,[115] 2007
Ciprofloxacin	2	Not performed	Seitz et al,[112] 2009
	0.02	0.02	Venturini et al,[115] 2007
Levofloxacin	5	Not performed	Seitz et al,[112] 2009
	5	0.05	Venturini et al,[115] 2007
	0.025	0.025	Empedrad et al,[80] 2003

*Although these concentrations are currently recommended for skin testing, there is controversy about nonirritating concentrations.

TABLE XIII. Recommended doses for drug provocation tests with quinolones*[109,112]

Quinolone	Doses administered at intervals of 30 min[109]	Doses administered at intervals of 60 min[112]
Moxifloxacin	5-50-100-100-150	25-50-100-200
Ciprofloxacin	5-50-100-150-200	50-125-250-500
Levofloxacin	5-50-100-150-200	50-125-250-500

*Increasing doses of the suspected fluoroquinolone were administered orally at intervals of 30 min or 60 min until reaching the full dose or until symptoms of a drug reaction occurred. Drug challenge protocols with less steps may also be considered such as 1/10th of the dose followed by the full dose.

and nonirritating dilutions were set at 0.05 mg/mL and 0.01 mg/mL, respectively. Mori et al[122] performed an allergy workup in children with histories of suspected clarithromycin and azithromycin hypersensitivity. Skin tests were performed to these drugs on both subjects and negative controls. The highest nonirritating concentrations used for the prick and intradermal tests were 50 mg/mL and 0.5 mg/mL, respectively, for clarithromycin and 100 mg/mL and 0.01 mg/mL, respectively, for azithromycin. There are concerns about false-positive and false-negative reactions associated with macrolide skin testing; therefore, graded challenge remains the criterion standard. Furthermore, clarithromycin is not available in intravenous form in the United States.

In vitro tests, such as BATs and lymphocyte transformation tests, and detection of macrolide-specific IgE antibodies have been used in several case reports, but they are yet to be standardized and are not commercially available.

Drug challenge tests remain the criterion standard to establish or exclude macrolide hypersensitivity.[16,118,123] Drug challenge can be performed for the suspected drug, a structurally related one, or an alternative substance; however, the challenge must always be carried out under strict medical surveillance and after a conscious assessment of a risk-benefit analysis on a per-patient basis. It is best performed as single-blinded, with increasing doses given every 30 minutes to achieve the maximum daily dose. Mori et al[122] used a 3-dose protocol, that is, 10%-20%-70% of the daily therapeutic dose on day 1, followed by a full-dose administration on day 2. In patients with a history of nonimmediate reactions, the challenge was continued for 5 days at a therapeutic dose.

Other macrolides. Nonantibiotic macrolides have also been involved in drug hypersensitivity reactions, ranging from allergic

TABLE XIV. Recommended ciprofloxacin desensitization procedure*[933]

Time (h)	Route	Ciprofloxacin concentration (mg/mL)	Volume given (mL)	Absolute amount (mg)	Cumulative total dose (mg)
0:00	IV	0.01	5.0	0.05	0.05
0:15	IV	0.1	1.0	0.1	0.15
0:30	IV	0.1	2.0	0.2	0.35
0:45	IV	0.1	4.0	0.4	0.75
1:00	IV	0.1	8.0	0.8	1.55
1:15	IV	1.0	1.6	1.6	3.15
1:30	IV	1.0	3.2	3.2	6.35
1:45	IV	1.0	6.4	6.4	12.75
2:00	IV	1.0	12.8	12.8	25.55
2:15	IV	10.0	2.5	25.0	50.55
2:30	IV	10.0	5.0	50.0	100.55
2:45	IV	10.0	10.0	100.0	200.55
3:00	Oral	NA	250-mg tablet		450.55

IV, Intravenous; *NA*, not available.
*The patient should take the next oral dose of 500 mg that evening.

contact dermatitis (ACD) due to topical application of tacrolimus in patients with atopic dermatitis, to generalized reactions elicited by systemic administration. Saito et al[124] performed a literature review on oral tacrolimus–related drug hypersensitivity reactions. Considering its immunosuppressive effects, it is not surprising that most patch-test results (but not all) were negative and most of these cases were diagnosed with a lymphocyte stimulation test.[124,125] Severe reactions, namely, hypersensitivity pneumonitis or DRESS, have been attributed (without drug hypersensitivity workup) to drug-eluting stents involving zotarolimus and everolimus, respectively.[126,127]

Management. Cross-reactivity among different macrolides has not been extensively studied, but when it was tested, most patients with a demonstrated hypersensitivity to a certain macrolide could tolerate another with a different number of atoms in the lactone ring.[80,116] Mori et al[122] reported double positivity in 2 patients with clinical histories of anaphylaxis to clarithromycin (14-C) and azithromycin (15-C). One of them had experienced anaphylaxis to both drugs, whereas the other one had never taken clarithromycin.

Macrolide antibiotics are unlikely to cross-react with macrolide immunosuppressants, such as 23-C tacrolimus and 29-C sirolimus. In a published case, cross-reactivity was suspected between clarithromycin and tacrolimus, but for both drugs, the assumption of drug hypersensitivity was based on clinical history alone and no specific workup was performed.[128]

Very few case reports of desensitization protocols to macrolides have been published (eg, to spiramycin in a pregnant woman suffering from toxoplasmosis or to clarithromycin in 2 patients infected by *Mycobacterium chelonae* and *Mycobacterium avium,* respectively) (Tables XV-XVII).[129-131] To our knowledge, there are no reports to date for other commonly prescribed macrolides, such as azithromycin and/or erythromycin.

Tetracyclines (by Stephanie Logsdon, MD)

General. Tetracyclines are a broad-spectrum antibiotic class of which 4 are available for systemic use in the United States: tetracycline, demeclocycline, doxycycline, and minocycline. In

TABLE XV. Desensitization protocol to spiramycin[130]

Day	Daily dose (IU)
1	300
	600
	900
	1,200
	3,000
	9,000
	12,000
	Total: 33,000
2	30,000
	60,000
	90,000
	120,000
	150,000
	180,000
	Total: 630,000
3	300,000
	600,000
	900,000
	1,200,000
	3,000,000
	Total: 6,000,000
4	3,000,000 thrice a day
	Total: 9,000,000
5	3,000,000 four times a day
	Total: 12,000,000

IU, International units.

addition, tigecycline is a glycylcycline, which is a new class of antimicrobials with similar antimicrobial activity as the tetracyclines. Adverse reactions involving IgE-mediated hypersensitivity are rare, and studies suggest that adverse reactions to minocycline are more common than to doxycycline. Differences in side-chain structures are hypothesized to be responsible.[132]

Major symptoms. For all tetracyclines, most hypersensitivity reactions are non—IgE-mediated, and include DRESS, papulosis, lupus-like reactions, serum sickness—like reactions, and photosensitivity.[133-136] Nonetheless, IgE-mediated reactions do occur, and anaphylaxis has been reported.[137-139] One report of drug fever secondary to tigecycline use has also been published.[140] Rates of cross-reactivity between tetracycline antibiotics are not established; however, 1 report includes a patient with doxycycline hypersensitivity who did exhibit cross-sensitization with minocycline.[141]

Diagnosis. For patients with suspected IgE-mediated reactions, skin testing is not standardized for any of the tetracycline antimicrobials, and positive and negative predictive values have not been established. One case report has noted positive skin prick testing result to full-strength tetracycline.[138] In addition, the minimum nonirritating concentration for intradermal testing in control subjects was 0.0002 mg/mL for minocycline and 0.001 mg/mL for doxycycline. The following step-wise skin testing protocols have been recommended: for minocycline, skin prick testing 0.2 mg/mL, intradermal testing 0.00002 mg/mL, intradermal testing 0.0002 mg/mL. For doxycycline, skin prick testing 10 mg/mL, intradermal testing 0.0001 mg/mL, intradermal testing 0.001 mg/mL.[142]

TABLE XVI. Oral clarithromycin desensitization protocol[129]

Step (15-min intervals)	Clarithromycin suspension (mg/mL)	Volume (mL)	Dose (mg)	Cumulative dose (mg)
1	0.05	0.1	0.005	0.0
2	0.05	0.2	0.01	0.0
3	0.05	0.4	0.02	0.0
4	0.05	1	0.05	0.1
5	0.05	2	0.1	0.2
6	0.05	4	0.2	0.4
7	0.5	0.8	0.4	0.8
8	0.5	1.6	0.8	1.6
9	0.5	3.2	1.6	3.2
10	0.5	6.4	3.2	6.4
11	5	1.2	6	12.4
12	5	2.4	12	24.4
13	5	4.8	24	48.4
14	50	1	50	98.4
15	50	2	100	198.4
16	50	4	200	398.4
17	50	8	400	798.4
18	50	10	500	1298.4

Management. In patients with low clinical suspicion for anaphylactic reactions and negative skin testing result, a graded drug challenge may be considered.[13] In cases of high suspicion for anaphylaxis or positive skin testing result where a tetracycline antibiotic is required, desensitization can be performed. There are no published reports of effective rapid desensitization protocols for these drugs, but some success has been seen with oral desensitization to minocycline and doxycycline. A 14-step protocol was used for minocycline, starting at 0.01 mg, followed by dose doubling at 30-minute intervals until the cumulative goal was reached. Furthermore, an oral desensitization protocol for doxycycline (Table XVIII) was successful, starting at 0.00001 mg and increasing in 10-fold steps every 30 minutes until 1 mg was reached, and then increasing by 2-fold increments until the goal dose was reached.[142]

Successful desensitization to tigecycline using a 12-step protocol has also been recently reported.[142]

Vancomycin (by Johnson Wong, MD)

General. Vancomycin is a tricyclic glycopeptide antibiotic that is used intravenously to treat various gram-positive cocci bacterial infections including those caused by methicillin-resistant *Staphylococcus aureus* and enterococcus, gram-positive cocci infections among patients with β-lactam hypersensitivity, and gram-positive cocci infections in patients with renal failure. Oral vancomycin is used to treat *C difficile* infections.

Major symptoms

"Red men syndrome". Red men syndrome (RMS) refers to flushing and pruritus, which are commonly induced by the rate-dependent direct mast cell degranulation (DMCD) effect of vancomycin. In severe cases, hypotension, bronchospasm, and urticaria may also accompany RMS. At a rate of 1 g/h or more, 10% to 80% of subjects developed RMS, whereas a much lower incidence occurred when the rate was reduced to 1 g over 2 hours.[143] Histamine is often elevated early on, whereas tryptase was not found elevated at 10 minutes. Treatment of choice of

TABLE XVII. Oral clarithromycin desensitization protocol*[131]

Dose no. (15-min intervals)	Concentration (mg/mL)	Dose (mL)	Dose (mg)
1	0.025	1.25	0.03
2	0.025	2.5	0.06
3	0.025	5	0.125
4	0.25	1	0.25
5	0.25	2	0.5
6	0.25	4	1
7	2.5	0.8	2
8	2.5	1.6	4
9	2.5	3.2	8
10	2.5	6.4	16
11	25	1.3	32
12	25	2.5	64
13	25	5	125
14	25	10	250
Cumulative dose			503

*Serial 10-fold dilutions of a clarithromycin suspension of 125 mg/5 mL (25 mg/mL) were performed to make clarithromycin solutions at 2.5, 0.25, and 0.025 mg/mL.

TABLE XVIII. Doxycycline oral desensitization protocol*

Step	Doxycycline (mg)	Cumulative dose (mg)
1	0.00001	0.00001
2	0.0001	0.00011
3	0.001	0.00111
4	0.01	0.01111
5	0.1	0.11111
6	1	3.11111
7	2	3.11111
8	4	7.11111
9	8	15.11111
10	12	27.11111
11	25	52.11111
12	50	102.11111
	Total time	360 min

*Steps with 30-min intervals. Lowest dilution was based on 1:100 dilution of the concentration that lead to positive skin testing result. Serial dilutions of doxycycline suspension were prepared with purified water.

mild to moderate RMS is to slow the infusion rate to half the previous infusion rate or 1 g per 2 hours or less, with antihistamine pretreatment.

Anaphylactoid reactions/anaphylaxis/severe refractory RMS. This may occur in a small subgroup of patients. Although an IgE-mediated mechanism is possible, most of these cases appeared to be a severe form of DMCD. Vancomycin-specific IgE measurement has not been reported in the literature. Skin testing has been proposed as a surrogate for both DMCD sensitivity and possible IgE-mediated sensitivity (see Skin Testing section below).[144-146] This highly sensitive group can generally receive a rapid continuous intravenous protocol as a method to induce temporary drug tolerance as described for vancomycin as well as other drugs.[147-150] Its advantage lies in the provision of continuous small increments that avoid periodic substantial increases in the rate of drug delivery. In several cases, one can reach a threshold level only the first day and the dose need to be gradually increased over several days. When possible, stopping concurrent narcotics or other agents that also have DMCD property may often allow a difficult desensitization to be successful.

Morbilliform rash/hematologic changes/DRESS. Morbilliform rash is relatively common and often occurs in isolation. It may also be accompanied by various combinations of fever, hematologic changes, and/or end-organ dysfunction. The hematologic changes commonly include eosinophilia and neutropenia, and rarely, leukemoid reaction, lymphocytosis, thrombocytopenia, lymphadenopathy, and vasculitis. The end organs that may be affected include kidney and liver. The combination of drug reaction, eosinophilia, and systemic symptoms constitutes the DRESS reaction, and a recent report indicated that HLA:A*32:01 is strongly associated with vancomycin-induced DRESS.[147] Another study suggested that circulating IFN-γ vancomycin-specific T cells may be isolated in such patients.[151] For patients who are receiving multiple drugs and develop these reactions, vancomycin should join β-lactam antibiotics high in the differential.[152] For patients with renal failure, vancomycin should be considered as a culprit agent, because of its long half-life, even if the reaction occurs weeks after the last dose. Management consists of drug withdrawal and supportive treatment.

Linear IgA bullous diseases/TEN. Vancomycin is the most commonly reported cause of the rare linear IgA bullous diseases that may present as TEN-like reactions.[153] In addition, TEN without identifying the mechanism has been reported. Management is drug withdrawal and supportive treatment. These reactions serve as absolute contraindication for readministration or desensitization.

Teicoplanin as alternative treatment. Teicoplanin is a similar glycopeptide antibiotic that is available only outside the United States. A major retrospective study and a prospective study from the same institution over different time frames showed that 12 of 117 (10%) and 14 of 24 (58%) patients, respectively, who had a hypersensitivity reaction to vancomycin also developed one to teicoplanin.[154,155] There was a high recurrence rate and new occurrence rate for neutropenia, leukopenia, and thrombocytopenia (10 of 14). Therefore, teicoplanin may not be an ideal alternative treatment option for patients with vancomycin hypersensitivity.

Skin testing and implications. Skin testing has been proposed as a surrogate for both DMCD sensitivity and possible IgE-mediated sensitivity. Polk et al[146] performed titration of vancomycin skin test reactivity as a function of vancomycin concentration in a group of 12 healthy male volunteers. At concentrations of more than or equal to 10 μg/mL (0.02 mL intradermally), all volunteers showed detectable wheal and flare. The area of the flare, but not the wheal size, increased with higher concentration, up to 40 to 100 μg/mL (0.02 mL intradermally) before reaching a plateau. Because these were healthy volunteers without previous vancomycin exposure, the wheal-and-flare responses were assumed to be due to DMCD at doses of more than or equal to 10 μg/mL (0.02 mL intradermally) and not an IgE-mediated mechanism. The size of the flare at 25 μg/mL (0.02 mL intradermally) correlated poorly with the area of flushing when the subjects were challenged with vancomycin infusion. Case reports of patients with "anaphylactoid/anaphylaxis/pruritus" who developed wheal and flare at vancomycin concentrations of 0.1 to 5 μg/mL (0.02 mL intradermally) on

skin testing were interpreted as representing IgE-mediated sensitivity.[144,145] However, the cutaneous reactivity, even at 0.1 μg/mL, may represent increased propensity for DMCD or increased sensitivity to the mast cell release products (induced by concurrent narcotic or due to intrinsic sensitivity of the patient).[150] Overall, the general consensus is that 50 mg/mL for skin prick testing and 0.005 mg/mL for intradermal skin testing are nonirritating concentrations (Table XIX).

Aminoglycosides (by Catherine Biggs, MD)

General. Aminoglycosides are a broad-spectrum class of antibiotics that are structurally composed of hydrophilic sugars possessing amine and hydroxyl functional groups.[156] Type IV hypersensitivity reactions in the form of ACD are commonly associated with aminoglycosides. The prevalence of ACD to neomycin sulfate reported by the North American Contact Dermatitis Group from 1985 to 2004 ranged from 7.2% to 13.1%.[157] Systemic contact dermatitis to aminoglycosides, as well as severe type IV hypersensitivity reactions such as TEN and DRESS syndrome, have also been described.[158-160] IgE-mediated reactions to aminoglycosides are uncommon but may occur after exposure to topical, inhaled, and systemic preparations.[161-163]

Major symptoms of hypersensitivity. IgE-mediated reactions described in the literature include urticarial reactions in response to both intravenous and inhaled tobramycin, as well as anaphylaxis to topical and systemic aminoglycosides.[161-163] ACD may present as erythematous/pruritic/edematous papules, plaques, and/or vesicles at the site of contact.[157] TEN caused by streptomycin has been associated with high fever, vomiting, and diffuse erythema, followed by extensive bullae formation and skin denudation.[159] Features of DRESS syndrome include a maculopapular and edematous skin rash, facial edema, and fever; laboratory studies may demonstrate eosinophilia, atypical lymphocytosis, abnormal liver enzymes, and coagulopathy.[158]

Diagnosis. IgE-mediated reactions are diagnosed on the basis of clinical features in keeping with an immediate hypersensitivity reaction, and have been confirmed in the literature using skin testing. Systemic reactions to epicutaneous and intradermal testing have been described in patients with a history of anaphylaxis to topical and systemic aminoglycosides, respectively.[161,164,165] Skin testing should therefore be approached with caution, and one may consider beginning with a 10-fold dilution for the first intradermal dose in patients with a history of anaphylaxis to an aminoglycoside (Table XX).

The diagnosis of type IV hypersensitivity reactions may be supported diagnostically by patch testing to the aminoglycoside in question. Significant cross-reactivity among aminoglycosides has been reported in ACD.[157]

Management. Avoidance of the offending agent is recommended for patients with a history of type IV hypersensitivity reactions. In the setting of negative skin testing result and low clinical suspicion for an IgE-mediated allergy, a graded challenge can be performed. Rapid desensitization is recommended for patients with an IgE-mediated allergy to an aminoglycoside who require the medication when no suitable alternative antibiotic exists.[167] Table XXI presents an example of a desensitization protocol for tobramycin.

TABLE XIX. Vancomycin rapid intravenous desensitization protocol*†

Time (h:min)	Vancomycin concentration (mg/mL)	Fluid infusion rate (mL/h)	Vancomycin infusion rate (mg/h)	Cumulative dose (mg)
0:00	0.0001‡	60.0	0.0060	0
0:15	0.001	20.0	0.020	0.0015
0:30	0.001§	60.0	0.060	0.0065
0:45	0.01	20.0	0.20	0.022
1:00	0.01	60.0	0.60	0.072
1:15	0.1	20.0	2.0	0.22
1:30	0.1	60.0	6.0	0.77
1:45	1.0	20.0	20	2.2
2:00	1.0	60.0	60	7.7
2:15	10	12.5	125	22
2:30‖¶#	10	25.0	250	54

*Adapted from the original protocol of Wong et al.[150]
†H_1 antihistamine pretreatment.
‡Typical starting concentration for patients with severe systemic reactions to previous vancomycin infusions.
§Typical starting concentration for patients with moderate systemic reactions to previous vancomycin infusions.
‖Continue at this infusion rate for the remainder of the dosage.
¶Minimize concurrent narcotic and other direct mast degranulators if possible.
#May need to stay just below a threshold vancomycin infusion rate the first day and advance as tolerated.

TABLE XX. Immediate hypersensitivity testing recommended for aminoglycosides[80,162,166]

Aminoglycoside	SPT dilutions (mg/mL)	IDT dilutions (mg/mL)
Gentamycin (preservative free)	40	0.04*
		0.4
		4
Tobramycin	40	0.04*
		0.4
		4

*Optional step that is recommended for patients with a history of anaphylaxis to an aminoglycoside.

Clindamycin (by Jocelyn R. Farmer, MD)

General. Clindamycin, a semisynthetic derivative of lincomycin, is a bacteriostatic agent that inhibits protein synthesis. It has been on the market since 1968 and is generally well tolerated. Common adverse reactions include a metallic taste in the mouth, transient elevation of transaminases, and a propensity for *C difficile* infection, with an increased risk for diarrhea (10%-23%) and pseudomembranous colitis (2%).[168]

Major symptoms of hypersensitivity. Immediate hypersensitivity to clindamycin is rare, though clindamycin-induced anaphylaxis has been reported.[169-171] Delayed hypersensitivity to clindamycin is much more common, initially estimated at 10% in small clinical studies from the 1970s, but revised to be less than 1% in a large retrospective chart review of clindamycin administration at a single US center from 1995 to 1997.[172-174] Delayed maculopapular exanthems are predominantly seen; however, SJS, DRESS, TEN, sweet syndrome, and AGEP have all been reported in the literature.[175-183]

TABLE XXI. Example of a desensitization protocol for intravenous tobramycin*[167]

Tobramycin				Full therapeutic dose = 100 mg IV q8h	
Tobramycin solutions†				1. 1 mg/200 mL NS (final concentration = 0.005 mg/mL) 2. 10 mg/200 mL NS (final concentration = 0.050 mg/mL) 3. 99 mg/200 mL NS (final concentration = 0.495 mg/mL)	
Step	**Solution**	**Rate (mL/h)**	**Time (min)**	**Administered dose (mg)**	**Cumulative dose (mg)**
1	1	2.5	15	0.0031	0.0031
2	1	5	15	0.0063	0.0094
3	1	10	15	0.0125	0.0219
4	1	20	15	0.0250	0.0469
5	2	5	15	0.0625	0.1094
6	2	10	15	0.1250	0.2344
7	2	20	15	0.2500	0.4844
8	2	40	15	0.5000	0.9844
9	3	10	15	1.2377	2.2221
10	3	20	15	2.4754	4.6975
11	3	40	15	4.9508	9.6482
12	3	80	136.875	90.3518	100.0000

IV, Intravenous; *NS*, normal saline; *q8h*, every 8 h.
*Dosage will vary on the basis of indication and patient weight.
†The total volume and dose dispensed of the tobramycin solutions are more than the final dose given to patient because the initial solutions are not completely infused.

Clindamycin-induced cytopenias have also been described, including anemia, neutropenia, and thrombocytopenia. The underlying mechanism is unclear, though direct myelosuppression at the level of the hematopoietic stem cell has been shown.[184]

Diagnosis. Immediate hypersensitivity skin testing to clindamycin has been studied. Skin prick at 150 mg/mL and intradermal injection at 15 mg/mL have been identified as nonirritating concentrations.[80,185] However, skin testing for immediate hypersensitivity to clindamycin was shown to be inferior to direct drug challenge in a study of 31 patients with a history of adverse clindamycin reaction, where 0 of 31 patients demonstrated a positive skin test result but 10 of 31 patients (32%) reacted during an oral challenge with 150 mg clindamycin.[185] The utility of immediate hypersensitivity skin testing to clindamycin in routine clinical practice has been questioned. In contrast, delayed hypersensitivity patch testing to clindamycin has been more promising. In patients with a predominant history of delayed maculopapular exanthems, patch testing via clindamycin 150-mg tablet pulverized and diluted in 1 mL saline or via pure clindamycin diluted to 10% in petrolatum resulted in positive reactions in 15% to 30% of patients, respectively.[186,187] Therefore, clindamycin patch testing may be useful in the context of a convincing history of delayed hypersensitivity.

Management. Most adverse reactions to clindamycin are mild and the drug can be continued safely. In cases of severe DHRs to clindamycin (eg, SJS, DRESS, TEN, and AGEP), the drug should be empirically avoided and there are no suitable alternatives. For nonsevere DHRs to clindamycin (eg, isolated maculopapular exanthem), a single case of oral desensitization has been described.[188] The DHR to clindamycin was confirmed on repeat oral challenge. The starting dose for the desensitization was clindamycin 20 mg every 8 hours, with dose escalation over 7 days as given in Table XXII. The patient was without adverse reaction at the 13-month follow-up, demonstrating proof of principle for clindamycin desensitization in the treatment of delayed drug hypersensitivity. More recently, clindamycin desensitization in the treatment of immediate drug hypersensitivity was reported in the literature in a single pediatric case using a rapid 9-step oral clindamycin desensitization protocol over 4 hours to a cumulative dose of 11 mg/kg per dose (300 mg/dose), which was then continued every 8 hours for the duration of the antimicrobial course.[189]

TABLE XXII. Protocol for clindamycin desensitization for the management of delayed hypersensitivity[188]

Day	Oral clindamycin dose (mg q8h)
1	20
2	40
3	80
4	150
5	300
6	600
7	600 (q6h)

q6h, Every 6 h; *q8h*, every 8 h.

Linezolid (by Jocelyn R. Farmer, MD)

General. Linezolid is an oxazolidinone that works by inhibiting the initiation of bacterial protein synthesis. It was first introduced for clinical use in the United States in 2000 and is generally well tolerated. Among the known adverse reactions, linezolid-induced cytopenias are best described and occur more frequently with long-term therapy (>14 days), increased daily dose (≥22 mg/kg), high serum concentration, and comorbidities including renal insufficiency.[190-193] Prevalence rates vary widely by study design but have been estimated at 15% to 50% for thrombocytopenia, 4.2% to 16% for anemia, and 2.2% to 4.5% for leukopenia.[194-196] The underlying mechanism is felt to be myelosuppression secondary to off-target inhibition of host protein synthesis in the bone marrow, which aligns with the dose-dependent and reversible nature of linezolid-induced cytopenias and the fact that linezolid-dependent antiplatelet antibodies have not been described.[197] Less frequent adverse reactions to linezolid include lactic acidosis, which typically occurs with long-term therapy (>6 weeks) and has been attributed to the underlying mitochondrial inhibitory mechanism of the drug.[198] In addition, there has been a case report of peripheral and optic neuropathy.[199-201]

Major symptoms of hypersensitivity. Immediate hypersensitivity to linezolid is rare. In a review of 828 linezolid treatment courses from 1997 to 2000, treatment-limiting dermatologic events including rash and pruritus occurred in 1.7% of cases, and only 2 patients had anaphylactic-type reactions.[194] Subsequently, a case of immediate urticaria and angioedema to linezolid and 2 more detailed descriptions of suspected linezolid anaphylaxis were reported in the literature.[202-204] Delayed hypersensitivity to linezolid is also infrequent and can include acute interstitial nephritis and/or

DRESS.[205-208] In a recent systematic chart review of 824 outpatients receiving monitored antibiotic therapy, linezolid was significantly associated with increased risk for peripheral eosinophilia but not end-organ damage including nephritis and DRESS.75 Together, these data suggest a known but small risk for severe DHRs after linezolid therapy.

Diagnosis. To date, no standardized immediate or delayed hypersensitivity skin testing protocols for linezolid have been published. Diagnosis is therefore limited to direct oral or intravenous challenge in cases in which it is clinically safe to do so.

Management. Treatment-limiting adverse reactions to linezolid include gastrointestinal complaints (with oral preparations), cytopenias, rash, and angioedema.[194,195] In cases of severe DHRs to linezolid (eg, acute interstitial nephritis or DRESS), the drug should be empirically avoided. Alternatively, for immediate hypersensitivity reactions, linezolid desensitization has been described.[202,203] Given that the drug has an oral bioavailability of approximately 100% in healthy volunteers, the first protocol used oral desensitization to linezolid. The patient tolerated 14 sequential dilutions in the absence of breakthrough symptoms.[203] More recently, intravenous linezolid desensitization for immediate hypersensitivity was accomplished as presented in Table XXIII. The patient had no breakthrough symptoms and subsequently made a transition to oral linezolid 600 mg every 12 hours to complete a 2-week course.

Nitrofurantoin (by Jocelyn R. Farmer, MD)

General. Nitrofurantoin is a broad-spectrum antibiotic that was first approved as clinical treatment for urinary tract infections in 1953. Intracellular nitroreductase produces the active drug metabolite, which functions to inhibit bacterial DNA and RNA synthesis.[209] Adverse reactions to nitrofurantoin are infrequent (5%-16%) and generally mild, reversible, and predominantly gastrointestinal (nausea and abdominal discomfort).[210]

Major symptoms of hypersensitivity. Immediate hypersensitivity reactions to nitrofurantoin are rare. Nitrofurantoin-induced anaphylaxis has been reported, and acute pulmonary reactions with symptoms consisting of shortness of breath, cough, fever, and peripheral eosinophilia within days to weeks of drug initiation have been reported at a rate of 1 in 5000 first administrations.[211-214] Lung pathology can demonstrate vasculitis, mild interstitial inflammation, eosinophils, and reactive type II pneumocytes.[215] In general, with drug discontinuation, patients have prompt recovery, and nitrofurantoin-induced acute pulmonary reactions have an overall mortality rate of only 0.5%.[216] Delayed hypersensitivity to nitrofurantoin can include pulmonary fibrosis, hepatotoxicity, erythema multiforme, erythema nodosum, agranulocytosis, megaloblastic anemia, and optic neuritis.[210] However, these adverse reactions are rare, with incidence rates per nitrofurantoin course previously calculated at 0.001% for all pulmonary reactions combined, 0.0003% for hepatotoxicity, 0.0004% for hematologic events, and 0.0007% for neurologic complications.[217] Nitrofurantoin-induced pulmonary fibrosis and hepatotoxicity have been associated with systemic autoantibody production and lymphocytic infiltrates to the end organ with subsequent risk for fibrosis.[215,218] An underlying mechanism of direct drug injury (via reactive oxygen species) and indirect drug injury (via induced cellular hypersensitivity) has been described.[219,220] In general, patients have pronounced recovery with drug cessation, though occasionally steroid therapy is also required.[215,218]

Diagnosis. To date, no standardized immediate or delayed hypersensitivity skin testing protocols for nitrofurantoin have been published despite a few case reports.[214,221] Diagnosis is therefore limited to direct oral challenge in cases in which it is clinically safe to do so.

Management. Most adverse reactions (eg, nausea and abdominal discomfort) are mild and the drug can be continued safely. However, in rare cases of severe nitrofurantoin-induced immediate hypersensitivity reactions (eg, anaphylaxis and acute pulmonary reactions), or DHRs (eg, pulmonary fibrosis and hepatitis), nitrofurantoin should be discontinued immediately and empirically avoided. Case reports of drug desensitization have not been described.

Antituberculous drugs (by Stephanie Logsdon, MD, and Josefina Cernadas, MD)

Introduction. Tuberculosis (TB), an infection caused by *Mycobacterium tuberculosis,* is a curable infectious disease, prevalent worldwide, and potentially fatal if proper treatment is not instituted. It remains a major cause of global mortality and morbidity. Most of the 2 billion people estimated to be infected with *M tuberculosis* have asymptomatic infection, termed latent TB infection.[222-224]

Similar to other *Mycobacterial* infections, treatment of TB requires simultaneous administration of multiple drugs. In the absence of bacterial resistance, treatment usually consists of isoniazid (INH), rifampicin, pyrazinamide (PZA), ethambutol (EMB), and streptomycin for 6 months.

Although most treatment courses progress with minor side effects, ADRs can occur. No consensus has been reached concerning the overall incidence of ADRs to these drugs. Different studies report an incidence of 5.5% to 57.8% according to different populations and ADR definitions.[225-230] Adverse effects or drug interactions can make it necessary to modify or discontinue treatment.

A major ADR to any of the anti-TB drugs, which implicates the discontinuation of that drug, can have severe implications. Alternative agents may lead to greater toxicity and are often less effective, frequently requiring longer treatment courses. As a result, the risk of treatment failure and relapse is higher in these cases. In these patients, management is further complicated by the difficult task of identifying the culprit agent for the reaction when they are on a typical multidrug regimen. In patients with SCARs, there are reports of further challenge with selected drugs because of the limited availability of treatment; however, as with any other SCAR, avoidance is typically recommended.[231]

Rifampin (Rifampicin). Rifampin remains a common therapy for latent and active TB, and is also used for infections with aerobic gram-negative organisms including the asymptomatic *Neisseria meningitidis* carrier state. It is rarely implicated in hypersensitivity reactions, ranging from pruritic skin eruptions to anaphylaxis, despite its frequent use, but is associated with multiple side effects.

Side effects of rifampin include an influenza-like syndrome, hepatotoxicity, skin exanthems, and induction of SMZ-TMP, which may cause significant drug-drug interactions.[232] The most commonly reported ADR is the influenza-like syndrome, which

TABLE XXIII. Protocol for linezolid desensitization for the management of immediate hypersensitivity[202]

Step	Bag (no.)	Bag (mg/mL in D5W)	Time	Rate (mL/h)	Infusion duration (min)	Monitoring duration (min)	Volume infused (mL)	Dose (mg)	Cumulative dose (mg)
1	1	0.02	0:00	18.0	5	10	1.50	0.03	0.03
2	1	0.02	0:15	42.0	5	10	3.50	0.07	0.10
3	2	0.20	0:30	9.0	5	10	0.75	0.15	0.25
4	2	0.20	0:45	18.0	5	10	1.50	0.30	0.55
5	2	0.20	1:00	36.0	5	10	3.00	0.60	1.15
6	2	0.20	1:15	72.0	5	10	6.00	1.20	2.35
7	3	2.00	1:30	13.8	5	10	1.20	2.30	4.65
8	3	2.00	1:45	28.2	5	10	2.30	4.70	9.35
9	3	2.00	2:00	56.4	5	10	4.70	9.40	18.75
10	3	2.00	2:15	112.5	5	10	9.40	18.75	37.50
11	3	2.00	2:30	225.0	5	10	18.80	37.50	75.00
12	3	2.00	2:45	450.0	5	10	37.50	75.00	150.00
13	3	2.00	3:00	300.0	15	10	75.00	150.00	300.00
14	3	2.00	3:25	600.0	15	30	150.00	300.00	600.00
Total time			4:10						

DSW, Dextrose 5% in water.

consists of fever, chills, headaches, myalgia, and rash. Published reports have also described rifampin hypersensitivity reactions in both adult and pediatric populations, ranging from pruritic skin eruptions to anaphylaxis.[233]

Diagnosis of rifampin hypersensitivity can be difficult, because many reactions are likely not IgE-mediated. Skin testing can be helpful in determining the likelihood of reaction, though negative skin test reactions do not indicate lack of sensitivity. Skin testing should be performed on the basis of published protocols in which the highest intradermal nonirritating drug concentration in nonallergic control subjects was 0.002 mg/mL.[234] Similar nonirritating intradermal concentrations have been reported in the literature for evaluation of rifampin hypersensitivity.[235]

Rifampin is a critical component of anti-TB therapy and often alternative drugs are not available. Therefore, in cases of hypersensitivity to rifampin, desensitization to the medication is often required. Recommended dosing of rifampin for TB is 600 mg daily, but maintaining a desensitized state with this dose can be problematic secondary to the drug's short half-life of 3 hours.[235,236] Despite this, various techniques for desensitization have been published, from rapid protocols to those of 7 or more days' duration.[235,237] Three pediatric case reports have been published.[238-240] Although uncommon, adverse reaction during rapid desensitization to rifampin may occur. In 1 previously published report, a pediatric patient developed a reaction during the protocol despite premedication, whereas the other 2 patients tolerated rapid desensitization without premedication. Another report described an adult patient who developed anaphylaxis during an oral desensitization procedure after positive skin testing result.[241]

A new, alternating-dose rapid oral desensitization protocol for rifampin was completed in a pediatric patient to achieve appropriate serum concentrations while safely maintaining the desensitized state.[240] The protocol used a regimen of 600 mg in the morning followed by 300 mg rifampin in the evening. This dosing was chosen because of the short half-life of rifampin, to maintain desensitization. For oral rifampin, the 13-step rapid oral desensitization protocol outlined in Table XXIV is effective and safe. Strict adherence to an every-12-hour dosing schedule is required to safely maintain the desensitized state.

Pyrazinamide. PZA, a synthetic pyrazine analogue of nicotinamide, is one of the most effective anti-TB drugs and is generally well tolerated. Like any other drug it may cause adverse reactions. These reactions are mainly toxic and may affect several organs: liver (cytolysis), joints (arthralgia), and the gastrointestinal system with nausea, vomiting, diarrhea, and abdominal pain. This drug may also induce more severe reactions such as nephrotoxicity, but the most severe one is hepatotoxicity ranging to fulminant hepatitis. Also, the drug most likely responsible for the occurrence of hepatitis during therapy for active TB is PZA.

Cutaneous manifestations are the most common reactions to PZA, though true allergic reactions are rare.[242-244] It can also be associated with early onset of maculopapular rash with pruritus, sometimes in association with dyspnea (possibly due to bronchospasm) and abdominal pain, suggesting anaphylactic/anaphylactoid reaction. The mechanisms underlying these reactions are undetermined.[225,245]

Among anti-TB medications, the incidence of serious side effects, defined as those requiring a documented change in therapy or hospitalization, is highest with PZA. These serious side effects are associated with female sex, older age, Asian origin, and HIV infection.[225]

Hypersensitivity reactions should be suspected if an immediate skin rash develops at the initiation of PZA treatment. If the degree of skin involvement is not severe, sequential reintroduction of the drugs first at low, then at full dosage may be attempted.

Bavbek et al[246] described an allergic reaction in a patient who had positive skin prick test (SPT) result to PZA, with negative results in 10 controls, and a positive oral challenge test result.[246] The SPTs were performed with PZA tablets at a concentration of 500 mg/mL along with a positive histamine control and a negative saline control 1 week after the initial reaction. The PZA tablets were smashed in a mortar and diluted with 1 mL of 0.9% NaCI. A positive reaction was seen only with PZA, producing a

TABLE XXIV. Rifampin oral desensitization protocol*[240]

Solution	Volume	Concentration
Solution A	10 mL	0.001 mg/mL
Solution B	10 mL	0.01 mg/mL
Solution C	30 mL	0.1 mg/mL
Solution D	10 mL	6 mg/mL
Solution E	15 mL	60 mg/mL

Step no.	Dose (mg)	Solution no.	Volume (mL)	Time (min)	Cumulative dose (mg)
1	0.0002	A	0.2	30	0.0002
2	0.002	B	0.2	30	0.002
3	0.02	B	2	30	0.02
4	0.2	C	2	30	0.2
5	2	D	0.3	30	2.2
6	4	D	0.7	30	6.2
7	8	D	1.3	30	14.2
8	16	D	2.7	30	30.2
9	30	E	0.5	30	60.2
10	50	E	0.8	30	110.2
11	100	E	1.7	30	210.2
12	150	E	2.5	30	360.2
13	250	E	4.2	30	610.2

*Full therapeutic dose administered 12 h after initiation of step 13.

wheal of 3 mm surrounded by erythema of 5 mm after 15 minutes.[246] The positive SPT result suggested an IgE-mediated mechanism, although *in vitro* measurement of PZA-specific IgE in the circulation was not conducted.

In cases of vital indication of this drug, when no alternative treatment is available, drug desensitization is an option (Table XXV).[225]

Isoniazid. INH is a bactericidal antibiotic against *M tuberculosis*. It acts by inhibiting mycolic acid biosynthesis. INH also disrupts DNA, lipid, carbohydrate, and nicotinamide adenine dinucleotide synthesis, and/or metabolism. The incidence of adverse reactions to INH in more than 2000 patients has been estimated to be 5.4%.[225,247]

Although the incidence of adverse reactions to INH is low, the best described are hepatic, neurologic, skin reactions, and fever.[248-253] Skin eruptions are rare, mild, and often transient, and usually consist of morbilliform and maculopapular rashes, urticaria, and pruritus.[254-256] Cutaneous reactions in patients receiving therapy are often difficult to diagnose because several drugs are frequently taken simultaneously. The liver is the most commonly affected organ and up to 20% of patients experience mild liver injury, which is usually subclinical and self-limited.[257] A less common form of reaction to INH is hepatitis, a more serious form of liver injury that can be fatal. The mechanism of liver damage is not completely understood, though it seems related to the direct toxicity of the drug.

The diagnosis is based on the regression of symptoms with discontinuation of the drug and the reproducibility with reintroduction. The reintroduction of antibiotics separately is necessary to identify the culprit(s). This approach to diagnosis cannot be done in the presence of severe reactions such as exfoliative dermatitis and hepatotoxicity. These are absolute contraindications for challenge.

TABLE XXV. Oral desensitization protocol with PZA[259]

Time (min)	Dose (mg)	Cumulative dose (mg)	Reactions
Day 1			
0	6.25	6.25	
30	12.5	18.75	
60	25	43.75	
90	50	93.75	
150	75	168.75	
210	125	239.75	
270	250	543.75	
Day 2			
0	500	500	
30	1000	1500	
Day 3			
0	750		
60	750	Total	

The rare cases of type I IgE-mediated allergic reaction require study with skin testing, with injectable forms for prick and intradermal tests.[258]

Rodrigues Carvalho et al[259] performed skin testing in a case of a generalized maculopapular rash, fever, and diarrhea after treatment with several anti-TB drugs. Prick test (PT) with INH was performed with an undiluted solution of 100 mg/mL and IDT with a 10 mg/mL concentration.

Several protocols have been published regarding the desensitization to INH based on adapted protocols from desensitization to penicillin (Table XXVI).[239,259-261]

Ethambutol. EMB is a bacteriostatic antimycobacterial drug most commonly used in combination with other drugs in the treatment of TB. The mechanism of action is not completely known. There is evidence that the drug exerts its bacteriostatic activity by inhibiting arabinosyltransferase, an enzyme that polymerizes arabinose into arabinan and then arabinogalactan, a mycobacterial cell wall constituent.

The dose of EMB is dependent on body weight, frequency of administration, and indication. It is generally well tolerated. Side effects are usually dose-related and more common when doses exceed 15 mg/kg.

The main side effect of EMB is ocular toxicity due to optic neuritis. Intermittent dosing may decrease the risk of ocular toxicity, as confirmed by Griffith et al[262] in a study of 229 patients treated with EMB for pulmonary *M avium* complex disease.

The combination of EMB with PZA for the treatment of latent TB in patients exposed to multidrug-resistant strains has been associated with a high incidence of hepatotoxicity or gastrointestinal intolerance, leading to discontinuation of therapy (~60% of treated subjects in 1 report).[263]

Hypersensitivity reactions to EMB such as rash and drug fever have been reported in 0.5% and 0.3% of patients, respectively.[264] Other reactions, such as dermatosis-like pigmentation, lichenoid eruptions, pulmonary infiltrates, and TEN, have also been described.[265-268]

In cases of severe reactions such as exfoliative dermatitis, oral challenge tests are not recommended. Skin and serological tests are usually unreliable, with single reports of positive patch-test

TABLE XXVI. Rapid oral tolerance induction protocol to isoniazid*[259]

Time (min)	Dose (mg)	Cumulative dose (mg)
0	0.050	0.050
20	0.10	0.15
40	0.25	0.40
60	0.50	0.90
80	1.00	1.90
100	2.00	2.90
120	4.10	8.00
140	8.20	16.20
160	16.30	32.50
180	30.60	63.10
200	50.30	113.40
340	100	213.40
480 (8 h)	150.00	363.40 (total daily dose)

*Serial dilutions of the 50 mg/5 mL suspension were prepared using purified water.

TABLE XXVII. General protocol for oral desensitization to EMB in adults*

Time from start (h:min)	EMB 1 mg/mL
0:00	0.1
00:45	0.5
01:30	1
02:15	2
03:00	4
03:45	8
04:30	16
05:15	32
06:00	50
06:45	100
07:30	200
11:00	400
Next day, 06:30	400 thrice a day

*Serial dilutions of the 50 mg/5 mL suspension were prepared using purified water.

results and positive lymphocyte stimulation test result to EMB.[254]

Skin prick and intradermal tests can be performed according to European Academy of Allergy and Clinical Immunology (EAACI) guidelines.[269] Immediate and late readings of IDT performed with sterile solutions of 1 mg/mL and 10 mg/mL are necessary because hypersensitivity reactions are mostly non−IgE-mediated. Immediate reading can be negative with late positive intradermal readings.[270] The decision to desensitize should be made in conjunction with the infectious disease specialist to determine the benefit of first-line therapy over alternatives, the duration of treatment, and the goals of therapy.

Drug desensitization should not be attempted in cases of severe skin reactions or those involving the mouth or mucous membranes (eg, exfoliative dermatitis and SJS). Tables XXVII, XXVIII, and XXIX summarize one institution's protocols that were used for several patients from the infectious disease department who had cutaneous hypersensitivity reactions to EMB.

Rodrigues Carvalho et al[259] described successful use of a modified 1-day temporary induction of tolerance protocol in a patient with reactions to several anti-TB drugs. The protocol consisted of a 2-fold increase in drug dose every 45 minutes until the desired total daily dose was reached.

Another protocol was used in a clinically non-IgE hypersensitivity reaction to EMB in which the previously described protocol was ineffective.[44] The patient had facial erythema, angioedema of the neck and upper limbs followed by a pruritic scaling maculopapular exanthem involving the neck, trunk, and upper and lower limbs, associated with mild dyspnea with no hemodynamic change 2 months before finishing treatment with EMB. Symptoms resolved after stopping the drug and reappeared after reintroduction. Skin tests were performed using solutions of 1 mg/mL and 10 mg/mL prepared from diluting a crushed 400-mg EMB tablet.[271] Immediate reading result was negative, but a positive intradermal reaction was present at 6 hours, with resolution at 72 hours. Because of the clinical presentation, positive delayed skin testing result, and reproducibility of the reaction on reexposure, a hypersensitivity reaction to EMB was diagnosed. The applied protocol was designed on the basis of the 12-step protocol by Castells et al (Table XXX), using slower dose increments and premedication with 25 mg of hydroxyzine and 40 mg of oral prednisone.[271,272]

TABLE XXVIII. Rapid oral tolerance induction to EMB*[259]

Time (min)	Dose (mg)	Cumulative dose (mg)
0	0.10	0.10
45	0.50	0.60
90	1.00	1.60
135	2.00	3.60
180	4.00	7.60
225	8.00	15.60
270	16.00	31.60
315	32.00	63.60
360	50.00	113.60
405	100.00	213.60
450	200.00	413.60
495	400.00	813.60
660 (11 h)	400.00	1213.60 (total daily dose)

*Serial dilutions of the 50 mg/5 mL suspension were prepared using purified water.

Streptomycin. Streptomycin is in the aminoglycoside class of medications and can be used to treat TB in combination with other medications. It works by blocking the ability of 30S ribosomal subunits to make proteins that result in bacterial death. Common side effects include dizziness, vomiting, numbness of the face, fever, and rash.[159]

Most ADRs due to intramuscular injection of streptomycin are gastrointestinal problems (38.09%), followed by skin reactions (30.48%) and hepatotoxicity (14.28%).[158]

Streptomycin is vestibulotoxic, ototoxic, and nephrotoxic. Nephrotoxicity can potentially interfere with the diagnosis of kidney malfunction. The most concerning side effects, as with other aminoglycosides, are nephrotoxicity and ototoxicity. Ototoxicity and nephrotoxicity are more likely to be found when therapy is continued for more than 5 days and at higher doses. In very high doses, streptomycin can also produce a curare-like effect with neuromuscular blockade that results in respiratory

TABLE XXIX. Desensitization protocol for EMB*[271]

Solution (mg/mL)	Time (min)	Dose (mL)	Dose (mg)	Cumulative dose (mg)
0.01	0	1	0.01	0.01
	30	2	0.02	0.03
	60	4	0.04	0.07
	90	8	0.08	0.15
0.1	120	1	0.1	0.25
	150	2	0.2	0.45
	180	4	0.4	0.85
	210	8	0.8	1.65
1	240	1	1	2.65
	270	10	10	12.65
10	300	10	100	112.65
	330	30	300	412.65

*Serial dilutions of the 50 mg/5 mL suspension were prepared using purified water.

TABLE XXX. Protocol for intravenous metronidazole desensitization*[289]

Step	Dose	Metronidazole concentration (mg/mL)	Volume (mL)
1	5 μg	0.005	1
2	15 μg	0.005	3
3	50 μg	0.05	1
4	150 μg	0.05	3
5	500 μg	0.5	1
6	1.5 mg	0.5	3
7	5 mg	5.0	1
8	15 mg	5.0	3
9	30 mg	5.0	6
10	60 mg	5.0	12
11	125 mg	5.0	25
12	250 mg	250 mg orally	Tablet
13	500 mg	500 mg orally	Tablets
14	2000 mg	2000 mg orally	Tablets

*Intravenous increments administered at 15- to 20-min intervals. Oral doses given 1 h apart.

paralysis. It is not recommended in patients with myasthenia gravis.[273]

In general, streptomycin has little allergenic potential, and hypersensitivity reactions are rare. However, skin rashes, eosinophilia, fever, blood dyscrasias, angioedema, exfoliative dermatitis, stomatitis, and anaphylactic shock have been reported.[274]

Sanchez-Borges et al[275] report that positive skin test results have been observed with streptomycin. However, a cautious approach must be taken when evaluating anaphylactic reactions to streptomycin, because systemic reactions have been observed after skin prick testing. The starting concentrations suggested for SPTs range from 0.1 to 1 mg/mL, gradually reaching the concentration of 20 mg/mL if tolerated. If SPT results are negative, intradermal testing can be performed and nonirritating concentrations of 4 mg/mL for intradermal testing have been established for gentamicin and tobramycin. There is no evidence of positive serum IgE to aminoglycosides. Patch tests with reading at 72 and 96 hours are recommended for the diagnosis of nonimmediate reactions. The concentration is 1% in petrolatum for streptomycin.[275]

In patients with streptomycin hypersensitivity, avoidance of the antibiotic is recommended. There are 2 reports of desensitization to streptomycin, one describing a 3-hour protocol with streptomycin beginning with 1 mg administered intravenously and the other consisting of streptomycin given intramuscularly, 10 mg, on the first day and doubled every day until it reached 800 mg, then 1.0 g, twice weekly.[276,277] Patients reached 1.0 g of streptomycin on the ninth day.

Metronidazole (by Sara Barmettler, MD)

General. Metronidazole is a 5-nitroimidazol compound that is active against a wide array of anaerobes, protozoa, and microaerophilic bacteria. Metronidazole is the treatment of choice for most anaerobic infections, including mild to moderate *C difficile* infections.[278] The 5-nitroimidazole drugs (including metronidazole or tinidazole) are the only class of drugs that provide curative therapy for trichomoniasis and thus, given the low efficacy of any drug other than the 5-nitroimidazole drugs, the Centers for Disease Control and Prevention guidelines recommend that patients with trichomoniasis who have experienced an IgE-mediated allergy to metronidazole and/or tinidazole be referred for desensitization rather than using an alternative class of drugs.[279]

Major symptoms. A number of nonallergic adverse effects of metronidazole have been described, including gastrointestinal symptoms, nervous system effects, genitourinary effects, and disulfiram-like reactions.[278] Hypersensitivity reactions caused by metronidazole appear to be rare, and case reports have been infrequently described in the literature. Several types of reactions have been reported, including immediate reactions and anaphylaxis, delayed reactions, fixed drug eruption, serum sickness–like reaction, and SJS/TEN.[280-285]

Diagnosis. Skin testing for metronidazole hypersensitivity has been described.[280,286] Skin prick testing was performed at a concentration of 125 mg/mL. Using this concentration, a patient tested in 1 study had previously suspected anaphylaxis to metronidazole and was positive on skin prick testing on 2 different occasions.[280] This case report also found skin prick testing result with metronidazole to be negative in 10 control patients.[280] In another case series, 4 patients with a history of cutaneous pruritic exanthemas were skin tested with prick testing at a concentration of 125 mg/mL of metronidazole followed by IDT with metronidazole at 0.5%, 5%, and 10%, with readings including delayed readings at 48 and 96 hours.[286] One patient had a positive result on the metronidazole SPT and did not undergo oral challenge. Oral challenge with doses of 250 to 500 mg provoked symptoms within 45 minutes to 1 hour in 2 patients and after 7 hours in the third. These patients were treated with intravenous corticosteroids and antihistamines with resolution. Ten control subjects who tested negative on skin prick testing passed an oral challenge to metronidazole in that study.[286] These results call into question the utility of skin testing to metronidazole.

Management. In patients who require metronidazole, but for whom there is documented positive skin testing result or a high clinical suspicion for immediate hypersensitivity reaction, and there are no alternative agents available or the alternative agents are not preferred (such as for trichomoniasis, as described before), desensitization can be performed. There are published

desensitization protocols for metronidazole via oral desensitization and intravenous desensitization.[287-289] Tables XXX and XXXI list the protocols for intravenous and oral desensitization, respectively. Desensitization protocols have proven to be very effective in a case series that found that oral and intravenous metronidazole desensitization regimens were 100% effective (15 of 15) in the management of trichomonas infection in women with nitroimidazole hypersensitivity.[290]

Patch-test data suggest some cross-reactivity between metronidazole and other imidazoles such as clotrimazole, ketoconazole, miconazole, and albendazole.[291-293] Therefore, in patients with a proven hypersensitivity reaction to metronidazole, avoiding theses agents is recommended if possible.

TABLE XXXI. Protocol for oral metronidazole desensitization*[288]

Step	Dose (mg)	Metronidazole concentration (mg/mL)	Volume (mL)	Cumulative dose (mg)
1	0.0025	0.025	0.1	0.0025
2	0.025	0.025	1	0.0275
3	0.25	0.25	1	0.2775
4	2.5	2.5	1	2.7775
5	25	2.5	10	27.78
6	250	250 mg	Tablet	277.8
7	750	750 mg	Tablets	1027.8
8	1000	1000 mg	Tablets	2027.8

*Doses given over the course of 1 d.

Antimalarials (by Sara Barmettler, MD)

General. Antimalarial drugs are used for the treatment and prophylaxis of malarial infection. Most antimalarial drugs target the erythrocytic stage of malaria infection, which is the phase of infection that causes symptomatic illness. There are several classes of antimalarial drugs including quinoline derivatives, antifolates, antimicrobials, and artemisinin derivatives. The antimicrobials used in malaria treatment and prophylaxis will not be described in this section.

Major symptoms. Quinoline derivatives include chloroquine, quinine, mefloquine, and primaquine. Chloroquine was one of the first antimalarials produced on a large scale; however, there is increasing resistance to chloroquine in many malaria-endemic countries. Commonly described side effects of chloroquine include headaches, dizziness, abdominal discomfort, vomiting, and diarrhea.[294] Chloroquine-induced pruritus has been described, most frequently in African populations, is transient (lasting 48-72 hours), and is not responsive to antihistamines.[295] Chloroquine has also been described to cause TEN, and other reactions including fixed drug eruption, bullous pemphigoid, exfoliative dermatitis, and exacerbation of psoriasis.[296,297]

Oral quinine is associated with cinchonism, which includes a number of unpleasant adverse effects including nausea, headache, tinnitus, dysphoria, and blurred vision.[297] Pruritus, skin flushing, and urticaria are associated with quinine hypersensitivity. Other cutaneous manifestations such as photosensitivity, cutaneous vasculitis, and lichenoid photosensitivity after quinine have been described in case reports.[297]

Mefloquine has been associated with a number of adverse effects including skin reactions such as pruritus (frequency of 4%-10%) and maculopapular rash (frequency of 30%).[298] Associations have also been drawn between mefloquine and urticaria, facial lesions, cutaneous vasculitis, SJS, and TEN.[298] Mefloquine is known to cause serious neuropsychiatric toxicity, including seizures, encephalopathy, and psychosis, which occur in 0.1% to 5% of patients treated for malaria.[299] Other adverse effects include vomiting and dizziness.[297]

Primaquine is the only 8-aminoquinoline in clinical use and is generally well tolerated. It can cause hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency, leukocytosis and leukopenia, and gastrointestinal upset.[297]

Antifolates include sulfonamides (including dapsone), pyrimethamine, and proguanil. Atovaquone/proguanil is an antimalarial combination with good efficacy and tolerability when used for prophylaxis and treatment. The most common side effects included headache, gastrointestinal symptoms of abdominal pain, anorexia, nausea, vomiting, diarrhea, and cough.[300,301] Atovaquone has been associated with SJS as well as acute eosinophilic pneumonia and maculopapular rash.[302,303] One case of anaphylaxis was described during clinical trials.[304] The combination of chloroquine and proguanil has also been described to cause AGEP and cutaneous vasculitis.[305,306] A rare but serious adverse effect is drug-induced hypersensitivity syndrome or DRESS. Up to 3.6% of dapsone recipients develop this syndrome, and as many as 13% of these die as a result.[307]

The artemisinin derivatives have excellent efficacy and safety, with very few attributable adverse effects.[308] One study reported an incidence of type I hypersensitivity reactions including urticaria and anaphylaxis at 0.03%.[309]

Diagnosis. There are rare case reports in which skin testing was used to evaluate for a type I hypersensitivity reaction to antimalarial agents. Unfortunately, there is no standardized nonirritating concentration of these drugs that both uses negative controls to establish nonirritating concentrations and identifies a positive case-control with a suggestive history. Specifically, skin prick testing has been described for atovaquone-proguanil, but the concentration used was not published and there was no mention of negative controls tested.[310] Similarly, in another case report, result of epicutaneous testing performed with chloroquine, proguanil, and mefloquine was negative, but again, there was no mention of the concentration used or whether there were negative controls. Patch testing for several antimalarial drugs (including malarone, proguanil, atovaquone, quinine, chloroquine, and mefloquine) has been described, with the drugs diluted at 30% in a petrolatum base.[303]

Management. In most literature describing hypersensitivity reactions, management includes cessation of the suspected culprit drug and selection of an alternate therapy. Given the large number of different classes of medications available for the treatment and prophylaxis of malaria, the selection of an alternative agent with equal efficacy generally has not provided an unsurmountable challenge, and thus there is a lack of specific oral challenge protocols or desensitization protocols available for antimalarial agents.

Antiparasitics (by Sara Barmettler, MD)

General. Antiparasitics are a class of medications used to treat diseases caused by nematodes, cestodes, trematodes, amoeba, and protozoa. The main type of antiparasitic drug is the antihelminthic group, which includes the antinematodes and

anticestodes. Within the antiparasitics, a number of adverse effects are associated with each drug, but case reports of hypersensitivity reactions are infrequent.

Major symptoms. Ivermectin is a semisynthetic derivative of avermectin and is useful in the treatment of a number of parasitic infections, including onchocerciasis, strongyloidiasis, ascariasis, trichuriasis, enterobiasis, scabies, head lice, and filarial worms.[311,312] Adverse effects include gastrointestinal upset, abdominal pain, fatigue, urticarial or maculopapular rashes, pruritus, and rarely, hepatotoxicity or neurologic side effects, and it has been implicated in a mucosal drug eruption with hemorrhagic scabs/erosions.[311,313-315] Ivermectin has also been described to cause a Mazzotti-type reaction (pruritus and adenopathy due to dying microfilaria) after the treatment of onchocerciasis.[311]

The benzimidazole class of antiparasitics includes albendazole, mebendazole, thiabendazole, and triclabendazole. Side effects of albendazole include abdominal pain, nausea, vomiting, and diarrhea, as well as rare side effects of transient transaminitis, agranulocytosis, and urticarial or other dermatologic manifestations.[316,317] Contact urticaria and contact dermatitis have been described in association with albendazole.[318] Albendazole has also been reported to cause fixed drug reaction.[319] The side-effect profile of mebendazole is similar to that of albendazole and includes gastrointestinal symptoms such as mild abdominal pain and diarrhea, as well as urticaria, pruritus, and edema.[320] More serious cutaneous manifestations have been reported with the combination of mebendazole and metronidazole, which was associated with an outbreak of SJS/TEN.[321] A number of adverse reactions have been described with the use of thiabendazole, including dizziness, nausea, vomiting, drowsiness, pruritus, headache, neuropsychiatric disturbances, hepatitis, and hypersensitivity reactions such as SJS.[320,322]

Praziquantel has activity against cestodes and trematodes including parasites such as schistosomiasis, intestinal tapeworms, cysticercosis, and other flukes. Side effects include headache, dizziness, drowsiness, nausea, and abdominal discomfort, and less commonly, itching/rash.[323] Although rare, hypersensitivity reactions to praziquantel have been described.[324-327] Interestingly, mouse model data have suggested that anaphylactic reactions may be induced by parasite antigen release rather than true hypersensitivity reactions to the praziquantel.[328]

Diethylcarbamazine is a piperazine derivative with activity against lymphatic filariasis, loiasis, and visceral larva migrans. Side effects include fever, headache, dizziness, gastrointestinal symptoms of abdominal pain and nausea, and urticaria/pruritus.[320] Administration of diethylcarbamazine in the setting of onchocerciasis is associated with a risk of precipitating the Mazzotti reaction (which includes symptoms of fever, urticaria, tender lymphadenopathy, tachycardia, arthralgias, edema, abdominal pain, and hypotension, and correlates with infection intensity).[329]

Antiprotozoals include eflornithine, melarsoprol, tinidazole, and metronidazole. Eflornithine is effective in the early and late central nervous system stage of infections with *Trypanosoma brucei gambiense* but not *Trypanosoma brucei rhodesiense*. Frequent side effects include diarrhea, anemia, leukopenia, and hair loss.[330] Melarsoprol is used to treat late-stage African trypanosomiasis. Use of melarsoprol is limited by its toxicity, which occurs commonly and includes severe adverse effects such as encephalopathy, polyneuropathy, exfoliative dermatitis, myocarditis, and hypersensitivity reactions such as bullous reactions.[330,331] Please see separate section on metronidazole for a detailed description of hypersensitivity reactions associated with the use of this drug. Antimalarials are also discussed in detail in a separate section.

Diagnosis. A few case reports describe the use of skin testing in the evaluation for a type I hypersensitivity reaction to antiparasitic agents. Skin prick testing and intradermal testing have been described for mebendazole and albendazole.[332] However, despite negative skin prick testing and intradermal testing results for mebendazole and albendazole, the patient in that case developed hives on oral challenge with both medications, thus suggesting a poor predictive value of this skin test.[332] Skin prick testing and intradermal testing have been described for praziquantel, and results for both were positive in the patient tested; however, that report did not mention the concentrations used or whether negative controls were used to establish nonirritating concentrations of the drug.[325] Patch testing for albendazole has been described, with 4 of 9 patients tested having positive results, though notably the patient with a clinical history of contact dermatitis did not test positive.[318]

Management. Management of hypersensitivity reactions in most cases reported involved cessation of the suspected culprit drug and selection of alternate therapy. Rarely, case reports have described desensitization to the antiparasitic agent. Desensitization has been described for praziquantel.[324,325] In 1 case, oral desensitization to praziquantel was attempted using a modified desensitization protocol with increasing doses of 30, 60, 100, 150, 300, 600, and 1200 mg administered 90 minutes apart. The patient described in this case did develop symptoms requiring hydrocortisone, antihistamine, and an H_2-blocker treatment during the desensitization, but was able to tolerate therapeutic doses of praziquantel given for 3 days subsequently.[325] In another case, desensitization was attempted using 13 doses of praziquantel at 15-minute intervals (first 6 doses were 18 mg each, the next 3 were 180 mg each, and the final 3 were 360 mg each). In this case, the patient developed generalized urticaria, difficulty swallowing, and chest tightness within 1 hour of his last dose. He was able to receive praziquantel on subsequent days without symptoms but was also given concomitant corticosteroids, so it was unclear whether true desensitization was achieved.[324] Oral challenge has been reported in the case of fixed drug eruption secondary to albendazole, with cross-reactivity reported with metronidazole.[319]

Antifungals (by Stephanie Logsdon, MD)

General. Antifungal medications including the azoles have been used in treatment and prophylaxis for various fungal infections for decades, while newer antifungal medications, including the echinocandin class, have gained increasingly widespread use in the treatment of pediatric and adult fungal infections. The azole drug class is composed of triazoles (including fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole) and imidazoles (including clotrimazole, ketoconazole, and miconazole). These drugs disrupt the fungal cell membrane through impairment of ergosterol synthesis.[333] Each drug in the azole class has distinctive indications for use, ranging from mucosal candidiasis to invasive mycoses. These drugs are

critical for managing the increasing frequency of fungal infections in all age groups, while offering a cost-effective option for prophylaxis in immunosuppressed patients.[334] Azoles are available in oral, intravenous, and topical formulations. Ketoconazole and miconazole are associated with increased rates of toxicity with administration, while newer triazoles have improved safety profiles and reduced drug-drug interactions, and are generally well tolerated in adult and pediatric patients. All azoles exhibit inhibition of the CYP450 enzymes.[333]

The echinocandin drug class includes micafungin and caspofungin, both of which inhibit β-(1,3)-D-glucan synthase. The frequency of invasive fungal infections is increasing in all age groups, thus escalating the need for effective therapies such as the echinocandins.[335] These medications have fewer adverse events and drug-drug interactions, and improved safety profiles over other antifungal agents. This is important because many patients who receive micafungin or caspofungin have other serious underlying medical illnesses. Both medications are administered intravenously, because their large molecular weight precludes acceptable gastrointestinal absorption. Importantly, neither agent appreciably affects the SMZ-TMP system, thus reducing the amount of drug-drug interactions.

Major symptoms of hypersensitivity. Hypersensitivity reactions have been reported for both azoles and echinocandins. The most common ADRs to the azole drug class include hepatotoxicity, skin exanthems, and gastrointestinal symptoms. In addition, each individual azole carries a distinctive side-effect profile.[333,334] Multiple case reports describe TEN, fixed drug eruptions, and other hypersensitivity reactions including anaphylaxis to fluconazole, voriconazole, and itraconazole.[336-339] Hypersensitivity to imidazoles, posaconazole, and isavuconazole is not well described. Common ADRs to the echinocandin drug class include transaminitis, electrolyte imbalances, fever, and skin exanthems.[340,341] There are single case reports describing the development of secondary TEN and hypersensitivity to caspofungin use in adult patients.[342,343] Beyond case reports, hypersensitivity to micafungin and caspofungin is not well described in the literature.

Diagnosis. Although skin prick testing for azoles is not validated, case reports have described protocols. Skin testing was performed in an adult patient with a history of anaphylaxis to voriconazole and 2 control patients. In this case report, testing comprised prick testing with 0.5 mg/mL and 0.05 mg/mL voriconazole with negative saline control. The patient had a positive result with the 0.5-mg/mL dilution, whereas both control patients had negative results to this dilution.[339] Skin testing to fluconazole has also been described in case reports. An adult patient who developed cutaneous and respiratory symptoms during treatment with fluconazole underwent intradermal skin testing with 0.2 mg/mL of the drug. Her skin test result was positive, whereas the skin test result was negative in a nonallergic control patient.[344] No further skin testing protocols are obtainable. Therefore, skin testing may be helpful for the diagnosis of hypersensitivity to azoles, but further investigation into ideal concentrations is needed.

Skin prick testing for the echinocandins is not well validated as well. Only 1 published description of skin testing to caspofungin was found during a literature review. Skin testing was completed on an adult patient with history of anaphylaxis to micafungin. This test included 1 intradermal injection of 0.05 mg caspofungin with a normal saline negative control.[343] No further skin testing protocols are available. Therefore, obtaining a complete clinical history remains critical in the diagnosis of echinocandin hypersensitivity because appropriate skin testing concentrations remain unclear.

Management. Drug desensitization protocols have been published for oral fluconazole, oral itraconazole, and intravenous voriconazole.[336,339] There is extensive variability in the protocols used for fluconazole desensitization, with protocol durations ranging from hours to days (Table XXXII).[337,338,344] For IgE-mediated allergy, preference should be given to desensitizations that occur over hours, rather than a prolonged protocol. No intravenous desensitization protocols for fluconazole are published. Each protocol was completed without significant systemic reactions, indicating that desensitization to azoles may be safely completed. Continued inquiry into the management of hypersensitivity to azole antifungals is necessary, because these medications continue to be critically required.

Micafungin and caspofungin are becoming critical therapeutic agents for patients with disseminated or virulent fungal infections, and thus these medications will likely be required in the future for use in patients who have hypersensitivity reactions to these medications. Drug desensitization may be an important tool for these patients. A recently published desensitization regimen used a standard 12-step protocol that has been successfully used with antibiotics such as penicillin (Table XXXIII).[345] The entire protocol was completed without reaction, and the patient completed the remainder of her therapeutic course uneventfully. This indicates that rapid desensitizations can be successfully completed in a safe and effective manner. Strict adherence to the dosing schedule is required to safely maintain the desensitized state. Further investigation into these medications will help physicians evaluate and manage echinocandin hypersensitivities.

Antivirals (by Tito Rodriguez, MD, and Elizabeth Phillips, MD)

Antiretrovirals

General. More than 30 antiretroviral (ART) drugs are currently available in the United States for the treatment of HIV-1, and these include 6 FDA-approved single-tablet regimens of 3 or more drugs as of March 2016. Six different categories of ART drugs (nucleoside reverse transcriptase inhibitors, nonnucleoside/tide reverse transcriptase inhibitors, protease inhibitors [PIs], entry inhibitors [including fusion inhibitors and CCR5 inhibitors], and integrase inhibitors) can be used in combinations of 3 or more drugs. Current treatment recommendations are to initiate combination ART drugs in all patients with HIV.[346-348] Nearly all ART drugs have been implicated in hypersensitivity reactions, usually presenting as delayed onset and ranging from the usual mild exanthem to less common life-threatening SJS/TEN or DRESS (Table XXXIV) reactions, with type I hypersensitivity reactions rarely seen.[349] These reactions can be confused by the presence of underlying opportunistic infections, immune restoration disease, or the fact that HIV-infected patients may take other drugs for prophylaxis of opportunistic infections that can also cause the full spectrum of clinically indistinguishable hypersensitivity reactions (eg, sulfamethoxazole/trimethoprim).

TABLE XXXII. Fluconazole oral desensitization protocol*[344]

	Fluconazole 200 mg			PO q24h
Full dose		197.76 mg		
Step	Concentration	Volume administered (mL)	Dose administered (mg)	Cumulative dose (mg)
1	0.02	1.00	0.02	0.02
2	0.02	2.00	0.04	0.06
3	0.02	4.00	0.08	0.14
4	0.2	0.80	0.16	0.30
5	0.2	1.60	0.32	0.62
6	0.2	3.20	0.64	1.26
7	2	0.75	1.50	2.76
8	2	1.50	3.00	5.76
9	2	3.00	6.00	11.76
10	20	0.60	12.00	23.76
11	20	1.20	24.00	47.76
12	20	2.50	50.00	97.76
13	20	5.00	100.00	197.76

PO, Per os (by mouth); *q24h*, every 24 h.
*Fifteen-minute intervals are given between doses. The first full dose is administered 24 h after completion of step 13.

TABLE XXXIII. Micafungin intravenous desensitization protocol*[345]

	Micafungin 150 mg	IV q24h	Total to be injected in each bottle (mg)
Full dose	150 mg		
Solution 1	250 mL of	0.006 mg/mL	1.5
Solution 2	250 mL of	0.06 mg/mL	15
Solution 3	250 mL of	0.595 mg/mL	148.82

Step	Solution	Rate (mL/h)	Time (min)	Administered dose (mg)	Cumulative dose (mg)
1	1	2	15	0.003	0.003
2	1	5	15	0.0075	0.0105
3	1	10	15	0.015	0.0255
4	1	20	15	0.03	0.0555
5	2	5	15	0.075	0.1305
6	2	10	15	0.15	0.2805
7	2	20	15	0.3	0.5805
8	2	40	15	0.6	1.1805
9	3	10	15	1.4882	2.6687
10	3	20	15	2.9764	5.6451
11	3	40	15	5.9528	11.5979
12	3	75	186	138.4021	150
Total time			351 min		

*The first full dose is administered 24 h after initiation of step 12.

Based on current evidence-based medicine, there should be no restrictions on who gets ART drugs and this should be considered in all patients after individual discussion and considerations presenting with HIV-1 regardless of $CD4^+$ T-cell count, viral load, or AIDS-defining illness history. From older data, hypersensitivity reactions have been described as occurring 100 times more commonly in HIV-infected patients than in the general population, but data from contemporary HIV populations are lacking.[349] In general, diagnosis of hypersensitivity reactions related to HIV therapy is made on the basis of clinical presentation, temporal relationship with drug exposure (typically 1-6 weeks), and exclusion of other etiologies.[346] Patients presenting with mild rash alone without fever or organ involvement can develop tolerance with continued dosing and uninterrupted treatment is recommended (eg, efavirenz and PIs).[349,350]

Major symptoms and management. Abacavir, a nucleoside reverse transcriptase inhibitor, is a common cause of severe hypersensitivity reactions, occurring in 2.3% to 9% of patients exposed to the drug.[349] The clinical syndrome of abacavir hypersensitivity includes fever, constitutional symptoms, and gastrointestinal disturbance. Rash is later in onset, and may be absent in up to 30% of patients.[349] These reactions have been associated with the presence of the MHC class I allele HLA-B*5701.[349,351-353] In clinical trials, HLA testing has shown 100% sensitivity of HLA-B*5701 for skin patch-test–confirmed abacavir hypersensitivity reactions as well as 100% negative predictive value; genetic screening for HLA-B*5701 has been part of guideline-based therapy before abacavir prescription since 2008.[349,351-353] A history of abacavir hypersensitivity reactions is an absolute contraindication to rechallenge, because subsequent reactions are often more rapid and severe than the initial reaction.[349,351-353]

Particularly with the advent of HLA-B*5701 screening, contemporary single-tablet regimens used as first-line ART therapy in clinical practice in the United States are associated with a very low risk of hypersensitivity reactions.

Abacavir hypersensitivity is unique compared with other drug hypersensitivity syndromes in that fever and malaise can develop within the first few days of initial dosing and with relatively late and inconsistent (70%) appearance of rash. The clinical symptoms, signs, and pharmacogenomics of other drug hypersensitivity syndromes are outlined in Table XXXIV.[349] Currently, abacavir is the only ART drug with an associated hypersensitivity for which a guideline-approved pharmacogenomic pretreatment and preventive screening strategy exists.[349] HLA-B*5701 testing before prescription of abacavir has become consistent practice in the developed world but is still not widely used in regions where either abacavir is not widely used (eg, Africa) or where the allele frequency of HLA-B*5701 is less than 1% (South and Southeast Asia, excluding Northern Thailand) and India where HLA-B*5701 carriage rate is as high as 10%.[353]

Immediate reactions have been rarely reported, and there are no standardized protocols for skin prick and intradermal testing.[354]

Anti–hepatitis C drugs. Hepatitis C virus (HCV) affects more than 170 million people globally. Traditional HCV treatment, which included pegylated IFN and ribavirin, had a low efficacy (45%) and has now been largely replaced by the direct-acting agents. In all HCV treatment regimens, the rates of rash were high, noted in up to 20% to 30% of cases.[349] Early direct-acting agents, such as the HCV NS3.4A serine PI telaprevir developed for genotype 1 HCV infection, in combination with ribavirin and IFN, have now largely been replaced with newer direct-acting agents. Telaprevir-associated rash was described in 50% or more of those initiating therapy, with more than 90% of these being mild to moderate eczematous rashes that were controlled symptomatically with antihistamines or topical corticosteroids and resulted in

TABLE XXXIV. Clinical manifestations, incidence, and pharmacogenomics of antiviral hypersensitivity syndromes[349]

Class	Agent	Reaction	Incidence	Treatment limiting	HLA association (population)
ART treatments[349]					
PIs	Atazanavir	Rash	≤6%	<1%	None known
	Darunavir	Rash	≤10%	<1%	None known
		SJS/TEN/DRESS	<1%	100%	None known
	Fosamprenavir	Rash—moderate to severe	≤19%	<1%	None known
	Lopinavir/ritonavir	Rash	2%	<1%	None known
	Tipranavir	Rash	≤10%	<1%	None known
NNRTIs	Efavirenz	Rash	4.6%-20%	<2%	HLA-DRB1*01 (French)
		SJS/TEN/DRESS	0.1%	100%	Not known
	Etravirine	Rash	≤10%	<2%	Not known
		DRESS/SJS/TEN	<0.1%	100%	Not known
	Nevirapine	Rash	4%-38%	6%	HLA-B*35:05 (Thai) HLA-C*04 (African, Asian, European, Thai) HLA-DRB1*01 (French) B*35:05, rs1576*G CCHR1 (Thai)
		DRESS	Up to 5%; 0.3%-1%	100%	HLA-B*14/C*08 (*Sardinian/Japanese*) HLA-B*35/C*04 (*SE Asian*) HLA-C*04 + CYP2B6 516 G-→ T (*European/Asian/African*) CYP2B6 (rs2054675, rs3786547, rs3745274) HLA-B*35:05/01 (*Thai/European*)
		SJS/TEN		100%	CYP2B6 G-→T HLA-C*04:01 (*African/Malawian*) CYP2B6 983 T→C (*Mozambique*)
		Hepatitis	<5%		HLA-DRB1*01:01 (*European*) HLA-DRB1*02:01 (*South African*) HLA-B*58:01 (*South African*)
	Rilpivirine	Rash	2%	<1%	None known
Fusion inhibitors	Enfuvirtide	Hypersensitivity reaction	<1%	Mostly for subcutaneous reactions not HSR	None known
NRTIs	Tenofovir	Rash	5%-7%	<1%	None known
	Abacavir	HSR (fever, GI symptoms, rash in 70%)	5%-8%	100%, hypotension, severe morbidity on rechallenge	HLA-B*57:01 (*European/black*) (100% negative predictive value, 55% positive predictive value)
		Rash only	3%	<1%	Not known
	Emtricitabine	Pruritus, rash	17%-30%	<1%	Not known
Integrase inhibitors	Raltegravir	Pruritus, diaphoresis, rash	2%-7%	<1%	Not known
		DRESS/SJS/TEN	<1%	100%	HLA-B*53:01 (African ancestry)[933]
CCR5 inhibitors	Maraviroc	Pruritus	3.8%	<1%	Not known

GI, Gastrointestinal; *HSR*, hypersensitivity reaction; *NRTI*, nucleoside reverse transcriptase inhibitor.

discontinuation in less than 10%. One study showed that in patients presenting with more than 50% body surface without DRESS/SJS/TEN, continuation with close monitoring was a safe alternative.[355] Less common reactions included DRESS in 5% and SJS/TEN in less than 1%. Newer direct-acting agents have infrequently been associated with skin rash. Simeprevir is a second-generation NS3/4A HCV PI that has been primarily associated with photosensitivity in up to 5% of patients, which may be dose-related. Simeprevir is codosed with sofosbuvir, which was not associated with phototoxicity in earlier trials when dosed without simeprevir. There have been no reports of photopatch testing that would accurately and reliably differentiate between phototoxicity and photosensitivity. Reports in the literature have been mixed, with early reports suggesting an allergic and a lichenoid pattern on histology favoring phototoxicity.[356,357] Diagnosis of anti-HCV drug hypersensitivity is based on clinical assessment of the syndrome.

Other antiviral drugs. Commercially available antivirals for herpes virus—acyclovir, valacyclovir, famciclovir, and penciclovir—have close chemical structures, and the alternative antiviral drugs available—foscarnet and cidofovir—present with relevant side effects. Hypersensitivity reactions to herpes virus antivirals are infrequent, usually consisting of contact allergy or delayed systemic reactions most frequently described for acyclovir.

Immediate reactions have been described, but skin testing is not well standardized and it has been described only in case reports with none or low number of controls.[358] Patch testing has been shown to be useful in case reports at 10% or higher concentration, but there are no data on its sensitivity and predictive values.[359] Other than abacavir there are no data on the diagnostic utility of patch testing for other antivirals. Cross-reactivity among structurally related acyclovir, valaciclovir, and famciclovir is partial, with approximately 50% of patients tolerating famciclovir after reaction to valacyclovir or acyclovir; therefore, challenge with a suitable alternative after a negative patch-test result must be considered before desensitization.[360]

Hypersensitivity reactions to influenza antivirals are limited to individual case reports that do not include details on cross-reactivities or skin testing standardization. Anaphylaxis and delayed reactions have been reported to oseltamivir.[361]

Desensitization. Desensitization protocols to ART drugs have been described for patients with severe delayed reactions limited to the skin where the specific antiviral agent was the only possible treatment for that patient (Table XXXV).[362,363] Although failures have been reported in several case reports with rapid desensitization protocols to enfuvirtide, it remains the preferred method due to the unknown risk of resistance with slow desensitization protocols.[362] If the rapid protocol fails, a published 2- to 3-day slow desensitization protocol can be used.[364] Because the mechanism underlying delayed antiviral hypersensitivity to most antivirals remains unclear, such slow protocols should be used with caution and only when no alternative therapeutic option is possible. Desensitization is contraindicated in patients who have experienced severe, life-threatening immunocytotoxic reactions, vasculitis, or bullous skin diseases such as SJS/TEN and DHS/DRESS and for abacavir in HLA-B*5701−positive patients.[270]

The role of skin testing or desensitization for HCV antivirals has not been determined, but 2 case reports have described slow desensitization protocols for ribavirin.[365] Desensitization has been described in immediate reactions confirmed by challenge and in some unclear delayed reactions for herpes simplex virus antivirals. No desensitization protocol to influenza antiviral treatment has been described.

CHEMOTHERAPEUTIC AGENTS

Carboplatin (by Sarita Patil, MD)

General. In oncology patients, repeated administration of platinum-based chemotherapeutic agents can result in the development of hypersensitivity.[366,367] In particular, the incidence of hypersensitivity reactions increases from 1% after the first dose of carboplatin to 27% after 7 doses.[366] The peak rate of hypersensitivity reactions occurs with the eighth or ninth dose, which often corresponds with the second or third cycle after restarting treatment for malignancy recurrence.[368] Drug desensitization has been found to effectively deliver carboplatin to patients with hypersensitivity.[272]

TABLE XXXV. Rapid subcutaneous (A) enfuvirtide desensitization protocol and (B) oral darunavir desensitization protocol

A*		B†	
Dose	Enfuvirtide	Dose	Darunavir
1	6.25 μg	1	25 μg
2	62.5 μg	2	250 μg
3	0.125 mg	3	500 μg
4	0.25 mg	4	1 mg
5	0.5 mg	5	2 mg
6	1 mg	6	5 mg
7	2 mg	7	10 mg
8	5.65 mg	8	25 mg
9	11.25 mg	9	50 mg
10	22.5 mg	10	100 mg
11	45 mg	11	200 mg
12	90 mg	12	300 mg
1-h interval between doses		30-min interval between doses	

*Adapted from DeSimone et al.[362]
†Adapted from Marcos Bravo et al.[363]

Major symptoms of hypersensitivity. Hypersensitivity reactions to carboplatin can range from mild cutaneous symptoms (flushing, pruritus, urticaria) to systemic anaphylaxis, defined as involving more than 2 organ systems, often with cutaneous, gastrointestinal, respiratory, and cardiac symptoms. Up to 50% of reactions include moderately severe reactions.[272] These reported hypersensitivity reactions do not include SJS, TEN, erythema multiforme, or serum sickness.

Diagnosis. In addition to a clinical history of reactions consistent with hypersensitivity, skin testing can aid in the diagnosis of carboplatin hypersensitivity. Standard carboplatin skin testing protocols use step-wise skin prick testing (10 mg/mL) and 3-step intradermal testing (0.1, 1, and either 3 or 5 mg/mL) with 0.02 mL, in addition to a positive control (0.1 mg/mL histamine base) and a negative control (saline). Higher intradermal skin testing concentrations (10 mg/mL) cause irritation and carry a risk of skin necrosis.[368] A positive skin test result can be defined as a wheal-and-flare reaction, with the wheal's greatest diameter being at least 3 mm larger than that seen with saline.[369]

Because of potential for false-negative skin testing results in certain patients, particularly in those with a recent history of anaphylaxis (within 4-6 weeks of skin testing), repeat skin testing is recommended for patients whose clinical history is consistent with a hypersensitivity reaction and who have a negative initial skin test result on evaluation. These patients' condition can be managed with desensitization while they are awaiting repeat skin testing.[369,370]

Management. In patients with carboplatin hypersensitivity, desensitization with a 12-step protocol (Table XXXVI) in a monitored setting (in an inpatient setting supervised by an allergy specialist) has been effective in delivering adequate chemotherapeutic doses to patients requiring therapy. A 13-step protocol similar to the 12-step protocol, with an additional 60 mL/h step between steps 11 and 12, can also be used.

Patients undergoing evaluation with repeat skin testing, because of a history of hypersensitivity reactions but with a negative initial skin test result, have also been able to safely receive their chemotherapeutic dose using a modified 8-step desensitization protocol (Table XXXVII). Antihistamine premedication is recommended before the use of these desensitization protocols.[368,369]

Low-risk patients who have a history of nonpruritic, nonblistering delayed rash or those who have a negative skin test result between 6 weeks and 6 months after their initial hypersensitivity reactions and who are therefore at a lower risk of having a falsely negative skin test result may be candidates to receive carboplatin by infusion at 50% of the standard infusion rate in an outpatient infusion center setting.[370]

For premedication, patients are advised to use 20 mg of oral cetirizine on the evening before desensitization, the morning of desensitization, and immediately before initiation of desensitization, but no data are available on optimal premedication regimens. In addition, before the start of the desensitization protocol, patients with initial skin symptoms such as pruritus or urticaria can be given oral or intravenous diphenhydramine 25 mg and oral ranitidine 150 mg (intravenous ranitidine 50 mg or famotidine can be substituted). Patients with mild cutaneous symptoms (flushing, erythema) as part of their hypersensitivity reactions may also benefit from premedication with oral aspirin 325 mg on the night before their desensitization and again 1 hour before their desensitization protocol begins.

During desensitization, hypersensitivity reactions are treated with cessation of the protocol and administration of intravenous diphenhydramine 50 mg for mild reactions. More severe or recurrent reactions are treated with intravenous methylprednisolone 60 mg, and systemic anaphylaxis should be treated with intramuscular epinephrine 0.3 mg. Once hypersensitivity reaction symptoms resolve, the desensitization can be resumed at a previous step and completed.

Oxaliplatin (by David Hong, MD)

General. Oxaliplatin is a third-generation platinum-based chemotherapeutic agent most commonly used to treat metastatic colon cancer in combination with leucovorin and fluorouracil (FOLFOX regimen). As with cisplatin and carboplatin, the risk of developing type I hypersensitivity reactions increases with successive exposures. Most patients develop reactions after the sixth treatment cycle, with the incidence being as high as 20%, comparable to that of carboplatin (incidence 27% after the sixth dose).[272]

Major symptoms of hypersensitivity. Symptoms of oxaliplatin hypersensitivity are typical of a mast cell–mediated process; common symptoms include flushing, pruritus, urticaria, and back pain. Cardiovascular and respiratory anaphylaxis is less common but has greater life-threatening potential. Less commonly, reactions featuring fever and chills/rigors with or without hypotension, nausea, and diarrhea have been described in case reports. IL-6 and TNF-α levels are often elevated acutely, and these reactions have been described as "idiosyncratic" or "cytokine storm–like."

Diagnosis. Oxaliplatin hypersensitivity appears to be predominantly IgE-mediated because skin testing using skin prick and intradermal testing appears to have a high negative predictive value, ranging from 80% to 100%, and a positive predictive value of 66% to 80% when skin prick and intradermal testing is performed. Typically, testing involves skin prick testing with oxaliplatin at 1 to 5 mg/mL, to be followed, if the result is negative, by intradermal testing using 10-fold serial dilutions starting at 10^{-2} and 10^{-1} dilutions and undiluted.[371-373] Symptoms of skin irritation, including injection-site pain and erythema, are more common with higher strengths of intradermal testing. In cases with a clinical history suggestive of type I hypersensitivity to oxaliplatin but negative skin test result, it may be appropriate to repeat testing after subsequent infusions of oxaliplatin, especially if there have been 8 or more previous lifetime exposures to oxaliplatin.[374] Conversion to a positive skin test result in such patients would deem them candidates for desensitization if continuing oxaliplatin therapy is desired.

Management. Type I hypersensitivity to oxaliplatin can be managed by desensitization in most cases. Various protocols have been used, with the total duration of infusion ranging from 90 minutes to 16 hours. Castells et al have described the greatest number of patients desensitized to platin-based chemotherapeutics using a 12-step protocol with three 10-fold dilutions of the drug given over approximately 6 hours. An example 12-step desensitization protocol is included in Table XXXVIII.

Most protocols premedicate patients with antihistamines to minimize the risk and/or severity of breakthrough reactions with desensitization. Additional premedication with a combination of aspirin and montelukast appears to be helpful for those patients whose reactions have prominently included flushing, thought to be mediated by the release of prostaglandins, and other inflammatory lipid mediators generated as a consequence of mast cell activation.

The literature describing idiosyncratic/cytokine storm–like reaction is quite limited, but management seems to revolve around intense premedication regimens of steroids with or without antihistamines.[375] Coadministration of intravenous fluids and infusion rate reduction have also been found to be useful interventions. The role for desensitization in this clinical scenario is not yet defined.

Taxanes (by Matthieu Picard, MD)

General. Immediate hypersensitivity reactions to paclitaxel and docetaxel occur in around 10% of patients, most commonly on first exposure, despite premedication with antihistamines and corticosteroids.[376-378] Nab-paclitaxel and cabazitaxel are less frequently associated with such reactions.[377] Cremophor-EL (contained in the paclitaxel formulation) and polysorbate 80 (contained in the docetaxel and cabazitaxel formulation) are thought to be responsible for immediate hypersensitivity reactions because they can cause complement activation and generate anaphylatoxins.[377] An IgE-mediated mechanism could also be responsible for some of these reactions.[378,379]

Major symptoms of hypersensitivity. Most immediate reactions are moderate in severity, with the most frequently reported symptoms being skin flushing, dyspnea, chest pain, and back pain.[376,378] In patients with hypotension, a serum tryptase level can be measured; an elevated level supports a mast cell–mediated reaction.[378]

TABLE XXXVI. Twelve-step carboplatin desensitization protocol*

Step	Solution	Concentration (mg/mL)	Rate (mL/h)	Time (min)	Administered dose (mg)	Cumulative dose (mg)
1	1	0.02456	2.5	15	0.0154	0.0154
2	1	0.02456	5	15	0.0307	0.0461
3	1	0.02456	10	15	0.0614	0.1075
4	1	0.02456	20	15	0.1228	0.2303
5	2	0.2456	5	15	0.307	0.5373
6	2	0.2456	10	15	0.614	1.1513
7	2	0.2456	20	15	1.228	2.3793
8	2	0.2456	40	15	2.456	4.8353
9	3	2.45666	10	15	6.0916	10.9269
10	3	2.45666	20	15	12.1833	23.1102
11	3	2.45666	40	15	24.3666	47.4768
12	3	2.45666	80	174.375	566.5232	614

*For a total dose of 614 mg carboplatin.

TABLE XXXVII. Eight-step carboplatin desensitization protocol*

Step	Solution	Concentration (mg/mL)	Rate (mL/h)	Time (min)	Administered dose (mg)	Cumulative dose (mg)
1	1	0.1656	5	15	0.207	0.207
2	1	0.1656	10	15	0.414	0.621
3	1	0.1656	20	15	0.828	1.449
4	1	0.1656	40	15	1.656	3.105
5	2	1.64358	10	15	4.109	7.214
6	2	1.64358	20	15	8.2179	15.4319
7	2	1.64358	40	15	16.4358	31.8677
8	2	1.64358	80	174.375	382.1324	414

*For a total dose of 414 mg carboplatin.

Paclitaxel and docetaxel can cause nonimmediate skin reactions with onset from 12 hours to 15 days after the infusion.[378] These reactions are most frequently characterized by flushing or by a maculopapular skin eruption.[378]

Although much less common, severe hypersensitivity reactions (SJS, TEN, acute interstitial pneumonitis, and subacute cutaneous lupus erythematosus) have been described in case reports in association with paclitaxel, docetaxel, and nab-paclitaxel.[377]

Diagnosis. Skin testing can be used to guide the method of reexposure: desensitization versus challenge in patients with an immediate taxane-induced hypersensitivity reaction.[378] Concentrations used for paclitaxel skin testing range from 1 to 6 mg/mL (SPT) and from 0.001 to 6 mg/mL (IDT).[378,380] False-positive results can occur at 6 mg/mL (IDT).[380] Concentrations used for docetaxel skin testing range from 4 to 10 mg/mL (SPT) and from 0.04 to 10 mg/mL (IDT).[378,380] Skin testing with cabazitaxel and nab-paclitaxel has not been reported.

Management. Following an immediate taxane-induced hypersensitivity reaction, reexposure through a regular or slowed infusion with or without additional premedication appears to be tolerated by many patients.[376,380,381] However, severe reactions were reported with this approach and desensitization can be used as an alternative, especially in patients with a positive skin test response and/or a moderate to severe initial hypersensitivity reaction (Figure 4).[376,378,380,381] The risk of recurrent reaction appears to decrease with repeated exposures, and desensitization protocols can be progressively shortened in patients with good tolerance to eventually perform a challenge and, if tolerated, resume regular infusions (Table XXXIX).[378,381]

Patients with a delayed skin reaction and a positive skin test response may be at risk of an immediate hypersensitivity reaction on reexposure and may require desensitization.[378] The risk of a recurrent delayed reaction also decreases with repeated exposures and many can eventually tolerate regular infusions.[378] In contrast, patients with severe nonimmediate hypersensitivity reactions (eg, SJS) should not be reexposed to taxanes.

Methotrexate (by Andrew MacGinnitie, MD, PhD, and Min Jung Lee, MD)

General. Methotrexate (MTX) is an antifolate chemotherapy and immunosuppressant agent that is used for the management of osteosarcoma, acute lymphocytic leukemia, and rheumatoid arthritis, along with other autoimmune diseases in adults and children. It inhibits the activity of dihydrofolate reductase, which is needed for *de novo* purine synthesis. Adverse effects, more commonly seen with high doses used in cancer therapy, include abdominal cramping, malaise, mucositis, myelosuppression, and renal and hepatic toxicity.[382] MTX pneumonitis that can progress to interstitial fibrosis has also been reported.[383] Although the incidence of hypersensitivity reaction is unknown, it is likely rare, and case reports of anaphylactic or anaphylactoid reactions have been described.[384,385]

Major symptoms of hypersensitivity. The signs and symptoms of hypersensitivity reactions have been seen with standard-dose, high-dose, oral, intramuscular, intrathecal, and/or

TABLE XXXVIII. Twelve-step desensitization protocol for oxaliplatin*

Target dose (mg)			Standard volume per bag (mL)	Final rate of infusion (mL/h)	Calculated final concentration (mg/mL)	Standard time of infusion (min)
500.0			250	80	2	187.5
			Total mg per bag			
Solution 1	250 mL of	0.020 mg/mL	5.000			
Solution 2	250 mL of	0.200 mg/mL	50.000			
Solution 3	250 mL of	1.984 mg/mL	496.065			

Step	Solution	Rate (mL/h)	Time (min)	Volume infused per step (mL)	Dose administered with this step (mg)	Cumulative dose (mg)
1	1	2.0	15	0.50	0.0100	0.0100
2	1	5.0	15	1.25	0.0250	0.0350
3	1	10.0	15	2.50	0.0500	0.0850
4	1	20.0	15	5.00	0.1000	0.1850
5	2	5.0	15	1.25	0.2500	0.4350
6	2	10.0	15	2.50	0.5000	0.9350
7	2	20.0	15	5.00	1.0000	1.9350
8	2	40.0	15	10.00	2.0000	3.9350
9	3	10.0	15	2.50	4.9607	8.8957
10	3	20.0	15	5.00	9.9213	18.8170
11	3	40.0	15	10.00	19.8426	38.6596
12	3	80.0	174.375	232.50	461.3405	500.0000
	Total time (min) = 339.375 = 5.66 h					

*The total volume and dose dispensed are more than the final dose given to patient because many of the solutions are *not completely infused*.

intravenous forms of MTX. The reactions can include pruritus, urticaria, angioedema, wheezing, dyspnea, hypotension, and/or loss of consciousness.[386,387] Although most reactions occur subsequently after the first exposure, hypersensitivity reactions occurring on first exposure have also been described.[388]

Diagnosis. The sensitivity and specificity of MTX skin testing as well as nonirritating skin testing concentrations have not been established. However, the following concentrations have been used for prick testing (10 mg/mL) and intradermal testing (0.1 mg/mL and 1 mg/mL).[386] Other skin testing concentrations with IDT (2.5 mg/mL), which were nonirritating in 2 healthy controls, have also been used in an adult patient.[389] Additional case reports in adults have demonstrated positive prick skin testing result.[390,391] In the pediatric population, a recent retrospective review of a single-center experience with MTX showed that only 1 of 4 patients tested positive on skin testing.[386] This may suggest immediate type I hypersensitivity as part of the pathogenesis in some patients.

Management. For patients with MTX reactions, the management should be individualized in the context of overall clinical picture after considering risks and benefits of reintroduction. If the patient has a negative skin testing result and/or history of minor reaction, challenge may be considered. The challenge can be performed starting with 1/100th of the total dose. Patients with severe reactions (especially involving vital sign changes, pharyngeal edema, respiratory and cardiovascular involvement, etc) should receive desensitization regardless of the skin test result. Case reports have described prolonged infusion ranging from 6 to 27 hours.[392-394] However, at some institutions, the current practice for both adults and children involves a desensitization protocol with 3 bags of different concentrations that are administered via 12 steps, with the first bag consisting of 1/100th of the total dose, the second bag 1/10th of the total dose, and the third bag containing the remainder of the dose. A 16-step protocol involving 4 bags has also been performed in cases with severe reactions. Each step involves doubling of the concentrations every 15 minutes until the last step (step 12) is reached. The premedications can include H_1 and H_2 antagonists in addition to leukotriene receptor antagonists and/or corticosteroids (Table XL).

Cyclophosphamide (by Rebecca Breslow, MD)

General. Adverse reactions to cyclophosphamide (CYC) are most commonly due to drug toxicity. The major determinant is the cumulative dose received; toxicities are related to both dose and duration of exposure to this agent. Major toxicities associated with CYC are bone marrow suppression, increased susceptibility to infection, gonadal toxicity leading to infertility, increased risk of hematologic and skin malignancies, cystitis, and bladder cancer.[395] Less common adverse reactions are described in several case reports, and are dermatologic. One patient with systemic lupus erythematosus treated with CYC developed a neutrophilic eccrine hidradenitis.[396] Another with multiple myeloma (MM) developed a neutrophilic folliculitis.[397]

Type I hypersensitivity reactions to CYC are relatively rare, but case reports can be found in the literature. Visitsunthorn et al[398] described a pediatric patient treated with CYC for systemic lupus erythematosus who developed urticaria on the fifth exposure to the agent. Skin testing result was negative, and the patient then underwent successful graded challenge. Rosas et al[399] described another pediatric patient with acute lymphoblastic leukemia, being treated with CYC/2-mercaptoethane sulfonate sodium who developed a maculopapular rash, diaphoresis, respiratory distress, and

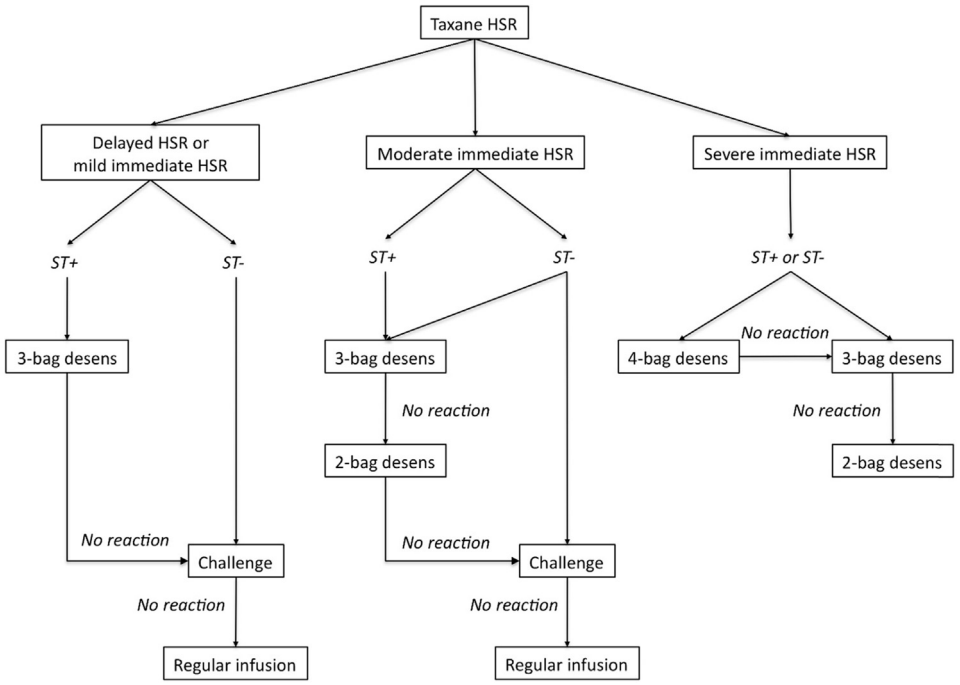

FIGURE 4. Approach to taxane reintroduction in patients with hypersensitivity reaction. Mild immediate hypersensitivity reactions present with symptoms that are limited to the skin (eg, flushing) or that involve a single organ/system and that are mild (eg, mild back pain). Moderate hypersensitivity reactions present with symptoms that involve at least 2 organs/systems (eg, flushing and dyspnea) but without a significant drop in blood pressure or in oxygen saturation. Severe hypersensitivity reactions present with symptoms that typically involve at least 2 organs/systems and with a significant drop in blood pressure (systolic ≤90 mm Hg and/or syncope) and/or in oxygen saturation (≤92%). In patients with a hypersensitivity reaction with desensitization or challenge, premedication can be adjusted for the next procedure, which can be administered using either the same or a longer protocol. Patients in whom the hypersensitivity reaction does not recur can then be treated with a shorter desensitization protocol, challenge, or regular infusion according to the algorithm. To ensure the patient's tolerance, each procedure can be repeated several times before proceeding with a shorter desensitization protocol, challenge, or regular infusion.

anxiety during his fourth cycle of CYC/2-mercaptoethane sulfonate sodium.[399] The symptoms resolved with steroid and antihistamine treatment. Skin testing result was also negative, but on rechallenge, the patient again presented with a similar rash. He underwent rapid desensitization, which he tolerated without a reaction, and was able to receive a subsequent treatment 2 days after his desensitization via standard administration.

Diagnosis. Type I hypersensitivity reaction to CYC is diagnosed on the basis of clinical history with or without skin testing. Signs and symptoms consistent with IgE-mediated hypersensitivity, such as hives, flushing, angioedema, pruritus, wheezing, and hypotension occurring during or shortly after receiving a dose of CYC, are highly suggestive of a type I hypersensitivity reaction. Skin testing can be used to confirm the clinical history; providers perform percutaneous prick testing with 10 mg/mL and intradermal testing with 1 mg/mL (1:10) and 10 mg/mL (1:1). In the case report by Visitsunthorn et al,[398] prick and intradermal testing was performed with 0.02 mL of the following dilutions of CYC: 1:100, 1:10, and 1:1. Rosas et al[399] also performed prick testing with 10 mg/mL and intradermal testing with 1 mg/mL. In all cases, prick and intradermal tests with CYC were compared with a histamine-positive control and a diluent-negative control, and results were determined on the basis of this comparison. Neither of these published studies included controls to determine optimal nonirritating skin testing concentrations for CYC.

Management. Patients with an equivocal history and negative skin testing result may be subjected to graded challenge. Visitsunthorn et al[398] described a successful graded challenge to CYC, in which the patient received antihistamine pretreatment and was challenged, with doubling of doses every 15 minutes; however, they did not include the number of doses received and quantity given with each dose.

Patients with a convincing clinical history with or without a positive skin test result may undergo rapid desensitization. Patients may be successfully desensitized using a standard 3-bag 12-step protocol, with premedication with H_1 and H_2 blockers (Table XLI).[272] Briefly, bag 1 contains a solution diluted 1:100, bag 2 a solution diluted 1:10, and bag 3 an undiluted solution. The rate of infusion is then doubled every 15 minutes until a threshold dose is reached; the patients may then receive the remainder of the undiluted bag 3 at a final rate of infusion of 80 mL/h. The protocol reported by Rosas et al[399] used an initial dose of 0.12 mg CYC diluted 1:4000, doubled every 15 to 30

minutes until a 1500-mg dose was delivered, for a cumulative dose of 2500 mg.

Doxorubicin (by Kathleen Lee-Sarwar, MD)

General. Doxorubicin is an inhibitor of DNA and RNA synthesis that intercalates between DNA base pairs, inhibits topoisomerase II, and leads to production of free radicals. Doxorubicin is available without liposomal encapsulation (trade name Adriamycin), in liposomal form (trade name Myocet), and in pegylated liposomal form (trade name Doxil). Liposomal encapsulation allows for preferential concentration in tumor tissue.

The nonliposomal form of doxorubicin is very rarely associated with hypersensitivity reactions. In contrast, the incidence of hypersensitivity reactions to pegylated liposomal doxorubicin is approximately 8%, with some series reporting up to a 25% incidence.[400] Reactions usually occur during the first cycle. The mechanism of hypersensitivity on first exposure may be explained at least in part by complement activation, which has been demonstrated *in vivo* during infusion of pegylated liposomal doxorubicin and may lead to mast cell activation.[400] Interestingly, in the setting of carboplatin hypersensitivity, combining carboplatin with pegylated liposomal doxorubicin appears to have a protective effect and is associated with reduced incidence of hypersensitivity reactions compared with carboplatin as a single agent or in combination with paclitaxel.[401]

Major symptoms of hypersensitivity. Typical clinical features include those of mast cell—mediated reactions such as flushing, pruritus, urticaria, dyspnea, sense of doom, and hypotension. Macular eruption and chest pain or back pain may also occur.[272] Hypersensitivity reaction severity ranges from mild to life-threatening.

Doxorubicin may also cause adverse effects that mimic, but are not, hypersensitivity reactions. Liposomal doxorubicin is associated with palmar-plantar erythrodysesthesia, also called hand-foot syndrome, which is a relatively common dermatologic toxic reaction associated with cytotoxic chemotherapy that can limit the use of such drugs. Definitive prevention and treatment strategies for palmar-plantar erythrodysesthesia have not yet been established. This typically occurs in the first 3 cycles of treatment.[402] Other cutaneous adverse effects include diffuse follicular rash, intertrigo-like eruption, and radiation recall dermatitis.[403] Acute cardiotoxicity is rare and may present with arrhythmias such as atrial fibrillation, acute heart failure, myocarditis, or acute myocardial infarction. Chronic cardiomyopathy is a more common and dose-limiting adverse effect.

Diagnosis. The ability to perform skin testing in the evaluation of doxorubicin hypersensitivity is limited by cutaneous toxicity.[404] Doxorubicin hypersensitivity is therefore generally diagnosed clinically, and there are no published skin testing protocols at this time.

Management. Desensitization has been successfully performed in patients with hypersensitivity reactions to doxorubicin and is an option for management when there is no effective alternative treatment.[271] In a report of 413 cases of rapid desensitization, desensitization to doxorubicin was successfully completed in a total of 29 patients. A 12-step rapid desensitization protocol may be used in cases with mild or moderate symptoms (Table XLII).[272] In the case of severe reactions including hypoxemia or hypotension, a 16-step rapid desensitization protocol should be used for the patient's first lifetime desensitization. If this is tolerated, a 12-step rapid desensitization protocol may be considered for subsequent infusions. Standard pretreatment includes a histamine H_2-receptor antagonist and a long-acting histamine H_1-receptor antagonist, with optional additional premedications tailored to the patient's initial reaction.

Pemetrexed (by Paige Wickner, MD)

General. Pemetrexed is an antifolate agent approved for use in patients with lung cancer and malignant pleural mesothelioma. The exact incidence of hypersensitivity reactions to pemetrexed is unknown. In phase III trials, 17% to 22% of patients receiving this agent developed a rash.[405] The literature includes case reports of pemetrexed-induced pneumonitis, pemetrexed-induced urticarial vasculitis, angioedema, AGEP, and anaphylactic reactions.

Diagnosis. The clinical symptoms should be closely evaluated and if IgE is suspected, skin testing and desensitization can be considered. If a more serious reaction occurred that is not felt to be IgE-mediated, alternative treatment options should be considered. Intradermal skin testing results with pemetrexed at dilutions of 1:10,000, 1:1,000, 1:100, and 1:10 have been reported. However, more data are needed to determine optimal nonirritating skin test concentrations.

Management. For patients with suspected IgE-mediated reactions with no reasonable alternatives, desensitization has been successfully reported (Table XLIII).

Lenalidomide (by Paige Wickner, MD)

General. Lenalidomide is an antiangiogenic agent that is primarily used for the treatment of MM, myelodysplastic syndrome, and mantle cell lymphoma. The exact incidence of hypersensitivity reactions to lenalidomide is unknown. The literature reports rashes occurring in 29% to 43% of patients, depending on underlying disease indication. A spectrum of rashes has been reported, including facial swelling, SJS, erythema multiforme, neutrophilic predominant rashes, and urticaria. Timing of reactions has been reported as both acute and delayed in onset.

Diagnosis. Clinical symptoms should be reviewed, evaluated, and continued, or alternative treatment options discussed. At present, there are no published nonirritating skin test concentrations for lenalidomide.

Management. There are case reports of desensitization to lenalidomide. An outpatient desensitization protocol used a starting dose of 2.5 mg and desensitized 5 patients to lenalidomide without adverse events. A shortened version of the outpatient desensitization can be repeated if the first desensitization has no adverse events (Tables XLIV and XLV). There are published rapid desensitization protocols for typical IgE-mediated symptoms as well as non—IgE-mediated symptoms.[406] Patients with evidence or suggestion of SJS/TEN or medication-induced laboratory abnormalities are not good candidates for desensitization.

TABLE XXXIX. Examples of desensitization and challenge protocols for paclitaxel (135-175 mg/m^2) infused every 3 wk over 3 h (example = 294 mg)

Four-bag/16-step protocol

Bag	Volume per bag (mL)	Concentration per bag (mg/mL)	Amount of bag infused (mL)	Dose infused per bag (mg)
Solution 1	250	0.00118	9.38	0.011
Solution 2	250	0.0118	9.38	0.111
Solution 3	250	0.118	18.75	2.213
Solution 4	250	1.167	250	291.665

Step	Solution	Rate (mL/h)	Time (min)	Volume infused (mL)	Dose infused per step (mg)	Cumulative dose (mg)
1	1	2.5	15	0.625	0.001	0.001
2	1	5	15	1.25	0.001	0.002
3	1	10	15	2.5	0.003	0.005
4	1	20	15	5	0.006	0.011
5	2	2.5	15	0.625	0.007	0.018
6	2	5	15	1.25	0.015	0.033
7	2	10	15	2.5	0.030	0.063
8	2	20	15	5	0.059	0.122
9	3	5	15	1.25	0.148	0.270
10	3	10	15	2.5	0.295	0.565
11	3	20	15	5	0.590	1.155
12	3	40	15	10	1.18	2.335
13	4	10	15	2.5	2.917	5.252
14	4	20	15	5	5.834	11.086
15	4	40	15	10	11.667	22.753
16	4	80	174.4	232.5	271.262	294.0
Total time (h) = 6.67						

Three-bag/12-step protocol

Bag	Volume (mL) per bag	Concentration (mg/mL) per bag	Amount of bag infused (mL)	Dose infused per bag (mg)
Solution 1	250	0.0118	9.38	0.111
Solution 2	250	0.118	18.75	2.213
Solution 3	250	1.167	250	291.676

Step	Solution	Rate (mL/h)	Time (min)	Volume infused (mL)	Dose infused per step (mg)	Cumulative dose (mg)
1	1	2.5	15	0.625	0.007	0.007
2	1	5	15	1.25	0.015	0.022
3	1	10	15	2.5	0.030	0.052
4	1	20	15	5	0.059	0.111
5	2	5	15	1.25	0.148	0.259
6	2	10	15	2.5	0.295	0.554
7	2	20	15	5	0.590	1.144
8	2	40	15	10	1.18	2.324
9	3	10	15	2.5	2.917	5.241
10	3	20	15	5	5.834	11.075
11	3	40	15	10	11.667	22.742
12	3	80	174.4	232.5	271.328	294.0
Total time (h) = 5.67						

Two-bag/8-step protocol

Bag	Volume (mL) per bag	Concentration (mg/mL) per bag	Amount of bag infused (mL)	Dose infused per bag (mg)
Solution 1	250	0.118	18.75	2.213
Solution 2	250	1.167	250	291.787

Step	Solution	Rate (mL/h)	Time (min)	Volume infused (mL)	Dose infused per step (mg)	Cumulative dose (mg)
1	1	5	15	1.25	0.148	0.148
2	1	10	15	2.5	0.295	0.443
3	1	20	15	5	0.590	1.033
4	1	40	15	10	1.18	2.213

(continued)

TABLE XXXIX. *(Continued)*

Step	Solution	Rate (mL/h)	Time (min)	Volume infused (mL)	Dose infused per step (mg)	Cumulative dose (mg)
5	2	10	15	2.5	2.917	5.130
6	2	20	15	5	5.834	10.964
7	2	40	15	10	11.667	22.631
8	2	80	174.4	232.5	271.369	294.0
Total time (h) = 4.67						

Challenge protocol

Bag	Volume per bag (mL)	Concentration per bag (mg/mL)	Amount of bag infused (mL)	Dose infused per bag (mg)
Solution 1	250	1.176	250	294

Step	Solution	Rate (mL/h)	Time (min)	Volume infused (mL)	Dose infused (mg) per step	Cumulative dose (mg)
1	1	2	15	0.5	0.588	0.588
2	1	8	15	2	2.352	2.940
3	1	80	185.625	247.5	291.06	294.0
Total time = 3.59 h						

Thalidomide (by Margee Louisias, MD, MPH)

General. Thalidomide is an immunomodulatory drug with antiangiogenic properties.[407] It is approved for use in erythema nodosum leprosum and MM, with off-label use in many conditions such as HIV apthous ulcers and graft-versus-host disease.[408] It is administered alone for erythema nodosum or in conjunction with dexamethasone for MM. Because of its known severe teratogenic effects it can be prescribed and dispensed only by prescribers and pharmacies enrolled in the THALOMID REMS program in the United States.[409] It is available as capsules in the United States. It is soluble at 25°C in dimethyl sulfoxide and sparingly soluble in water and ethanol. The incidence of thalidomide hypersensitivity reactions ranges from 6.3% to 47.7% among several thalidomide clinical trials.[407]

Major symptoms. Thalidomide hypersensitivity presents with delayed (usually within first month of treatment) skin reactions of varying severity.[407] However, in a retrospective review, skin reactions were seen more than 12 weeks after initiation with thalidomide or thalidomide analogs (lenalidomide, pomalidomide), in the setting of dose escalation or steroid tapering.[410] Dry skin, pruritic maculopapular rash, morbilliform rash, diffuse erythematous eruptions, scaling erythroderma, eosinophilia, and TEN/SJS have been described in the literature.[407,411] Body distribution is variable but is reported to mostly affect the trunk and proximal limbs.[407]

Diagnosis. There is no standardized skin testing or patch testing protocol available. Nucera et al[412] performed prick-by-prick testing with a solution made from a tablet dissolved in saline. However, because thalidomide (capsule) is soluble only in dimethyl sulfoxide, which is a skin irritant, skin prick testing can be done only with thalidomide dissolved in saline in accordance with European Network of Drug Allergy/EAACI (ENDA/EAACI) guidelines.[79] Nucera et al[412] also performed intradermal testing with thalidomide at a concentration of 0.04 mg/dL. Patch testing was also done according to ENDA/EAACI and American Academy of Dermatology guidelines. Patches were applied to the interscapular area with commercially available adhesive anallergic gauze strips and assessed at 48 and 72 hours.[269,413] Saline and histamine were used as negative and positive controls for all testing, respectively; however, whether these concentrations are nonirritating was not established.

Management. The challenge protocol given in Table XLVI is adapted from Nucera et al[412] who performed it in an ambulatory setting. The patient experienced a pruritic, erythematous rash after completion of day 2. Symptoms improved with an antihistamine. The desensitization protocol is also adapted from Nucera et al,[412] who performed it over 5 days in a hospital setting (Table XLVII). The same patient underwent desensitization without adverse reaction and completed treatment without any issues. Oral antihistamine was used as premedication.

Tyrosine kinase inhibitors (by Joyce Hsu, MD)

Since the introduction of imatinib in 2001, the tyrosine kinase inhibitor (TKI) family of therapeutics has continued to expand rapidly. Currently, there are 31 FDA-approved medications in this family, including (with targets) the following[414,415]:

- ALK: crizotinib, ceritinib, alectinib, and brigatinib
- BCR-Abl: bosutinib, dasatinib, imatinib, nilotinib, and ponatinib
- BTK: ibrutinib
- c-Met: crizotinib and cabozantinib
- Epidermal growth factor receptor (EGFR) family: gefitinib, erlotinib, lapatinib, vandetanib, afatinib, and osimertinib
- JAK family: ruxolitinib and tofacitinib
- PDGFR alpha/beta: axitinib, gefitinib, imatinib, lenvatinib, nintedanib, pazopanib, regorafenib, sorafenib, and sunitinib
- RET: vandetanib
- Src family: bosutinib, dasatinib, ponatinib, and vandetanib
- Vascular EGFR family: axitinib, lenvatinib, nintedanib, regorafenib, pazopanib, sorafenib, and sunitinib

TKIs are used in the treatment of numerous malignancies and myeloproliferative disorders, as well as hypereosinophilic syndrome and aggressive systemic mastocytosis in the case of imatinib. As a family, they are associated with significant cutaneous and systemic side effects that are important to differentiate from true hypersensitivity.

TABLE XL. Samples of 2 desensitization protocols for MTX*

Step	MTX (mg/mL)	Volume infused per step (mL)	Dose administered with this step (mg)	Cumulative dose (mg)
Twelve-step protocol				
1	0.002	0.5	0.001	0.001
2	0.002	1.25	0.0025	0.0035
3	0.002	2.5	0.005	0.0085
4	0.002	5	0.01	0.0185
5	0.02	1.25	0.025	0.0435
6	0.02	2.5	0.05	0.0935
7	0.02	5	0.1	0.1935
8	0.02	10	0.2	0.3935
9	0.2	2.5	0.4961	0.8896
10	0.2	5	0.9921	1.8817
11	0.2	10	1.9843	3.866
12	0.2	232.5	46.134	50
Sixteen-step protocol				
1	0.0002	0.5	0.0001	<0.001
2	0.0002	1.25	0.00025	<0.001
3	0.0002	2.5	0.0005	0.001
4	0.0002	5	0.001	0.002
5	0.002	0.5	0.001	0.003
6	0.002	1.25	0.0025	0.005
7	0.002	2.5	0.005	0.010
8	0.002	5	0.01	0.020
9	0.02	1.25	0.025	0.045
10	0.02	2.5	0.05	0.095
11	0.02	5	0.1	0.195
12	0.02	10	0.2	0.395
13	0.2	2.5	0.4961	0.891
14	0.2	5	0.9921	1.883
15	0.2	10	1.9843	3.867
16	0.2	232.5	46.134	50.000

*Goal dose of MTX was 50 mg via intravenous administration. Premedications include H_1 and H_2 antagonists with or without a leukotriene receptor–blocking agent with or without corticosteroids. Interval of 15 min between steps and the rate of infusion at the last step is continued until the end of infusion.

Skin rash—often erythematous and papular or pustular—is commonly associated with TKIs, particularly EGFR inhibitors (up to 100% of patients).[416] Because of the association between EGFR- and vascular endothelial growth factor and its receptor–associated rash development and improved survival outcomes, supportive care with steroids, antihistamines, and antibiotics is preferable in many cases.[417] Hand-foot skin reaction, characterized by pain and blistering on the palms and soles, is associated with sorafenib, sunitinib, and other vascular EGFR inhibitors. It occurs generally in the first 2 to 4 weeks of treatment. Oral dysesthesia and mucositis occurs with TKIs, particularly sorafenib and sunitinib, and may occur simultaneously with skin rash and hand-foot syndrome.[418] Mucosal involvement may also include conjunctivitis with EGFR inhibitors and periorbital edema with imatinib. These symptoms can be difficult to differentiate from systemic drug reactions, and skin biopsy can be helpful.[419]

Diarrhea is also observed commonly with TKIs as a class. Several of the TKIs, such as lapatinib, sunitinib, and pazopanib, carry a black box warning for liver toxicity, but it occurs commonly with other TKIs including gefitinib.[420] Dose reduction or drug discontinuation should be considered with hepatotoxicity as well as severe and chronic diarrhea.[419] Desensitization protocols have been described for several TKIs.

Imatinib. Ten patients with imatinib hypersensitivity who underwent subsequent desensitization were described by Nelson et al[421] in 2006. These patients had predominantly cutaneous initial reactions, though several had additional fever, blistering, edema, or diarrhea. One patient was skin tested by skin prick testing at 0.01 and 0.1 mg/mL and intradermal testing at 0.001 mg/mL, 0.01 mg/mL, and 0.1 mg/mL. Erythema was reported on intradermal testing. Of these 10 patients who completed a 4-hour rapid oral desensitization (Table XLVIII), 8 were subsequently able to tolerate daily imatinib without hypersensitivity symptoms. The other 2 patients developed rash hours to days after desensitization.

Subsequently, Paolo[422] published a case report describing slow oral desensitization to imatinib over 23 days for a patient who developed eosinophilic dermatitis after 6 weeks (Table XLIX). Skin testing result was negative, using skin prick 0.1 mg/mL, and intradermal testing with 0.0001 mg/mL, 0.001 mg/mL, 0.01 mg/mL, and 0.1 mg/mL imatinib. Patch testing was also performed, and the result was negative using 0.1 mg/mL imatinib in 5% petrolatum. For the rapid oral desensitization, same-day dose increases were administered every 20 minutes. The patient initially failed rapid desensitization twice, but was able to tolerate imatinib after slow oral desensitization (Table XLIX).

Crizotinib. Rash with crizotinib occurs in about 10% of patients, and is generally mild to moderate in severity. Hypersensitivity reactions are rare, but reported. Sanchez-Lopez et al[423] described a patient presenting with urticaria and facial edema for more than 40 days after initiation of treatment. Skin testing was performed with crizotinib capsules suspended in water (skin prick 25 mg/mL, intradermal testing 0.025 mg/mL and 0.25 mg/mL) and the result was negative. Five normal controls also had negative results to skin testing with this regimen. The patient was premedicated with intramuscular dexchlorpheniramine 5 mg and methylprednisolone 40 mg, and the 5-step oral desensitization was performed with 30-minute intervals and 120 minutes of observation on completion (Table L). The patient subsequently tolerated crizotinib without hypersensitivity symptoms.

In 2014, Awad et al[424] also described 2 patients with more rapid-onset crizotinib hypersensitivity, one with immediate urticaria and edema and the other with a delayed maculopapular rash. Patients were premedicated 1 hour and 12 hours before desensitization with 10 mg of loratadine and 10 mg of cetirizine. Both patients were successfully desensitized to crizotinib using a 12-step rapid desensitization protocol, with 15-minute intervals between steps (Table LI).

Sorafenib. Sorafenib is more commonly associated with hand-foot skin reaction and other symptoms related to toxicity, but it can rarely (<1%) trigger allergic symptoms, including urticaria. In 2008, Bauer et al[425] described a patient who developed a pruritic generalized maculopapular rash after 2 weeks of sorafenib therapy. The rash resolved with discontinuation of sorafenib and treatment with oral antihistamines and topical steroids. They

TABLE XLI. Twelve-step desensitization protocol for CYC*

Target dose (mg)	Standard volume per bag (mL)	Final rate of infusion (mL/h)	Calculated target concentration (mg/mL)	Standard time of infusion (min)
1000	250	80	4	187.5
		Total mg per bag		
Solution 1	250 mL of 0.040 mg/mL	10.000		
Solution 2	250 mL of 0.400 mg/mL	100.000		
Solution 3	250 mL of 3.969 mg/mL	992.130		

Step	Solution	Rate (mL/h)	Time (min)	Volume infused per step (mL)	Dose administered with this step (mg)	Cumulative dose (mg)
1	1	2.0	15	0.50	0.0200	0.0200
2	1	5.0	15	1.25	0.0500	0.0700
3	1	10.0	15	2.50	0.1000	0.1700
4	1	20.0	15	5.00	0.2000	0.3700
5	2	5.0	15	1.25	0.5000	0.8700
6	2	10.0	15	2.50	1.0000	1.8700
7	2	20.0	15	5.00	2.0000	3.8700
8	2	40.0	15	10.00	4.0000	7.8700
9	3	10.0	15	2.50	9.9213	17.7913
10	3	20.0	15	5.00	19.8426	37.6339
11	3	40.0	15	10.00	39.6852	77.3191
12	3	80.0	174.375	232.50	922.6809	1000.0000
Total time (min) = 339.375 = 5.66 h						

*The total volume and dose dispensed are more than the final dose given to patient because many of the solutions are *not completely infused*.

TABLE XLII. Example 12-step/3-bag desensitization doxorubicin protocol

Target dose	58 mg
Standard volume per bag	250 mL

Solution	Volume per bag (mL)	Concentration (mg/mL)	Total dose per bag (mg)
Solution 1	250	0.00232	0.58
Solution 2	250	0.0232	5.8
Solution 3	250	0.23017	57.543

Step	Solution	Rate (mL/h)	Time per step (min)	Dose administered per step (mg)	Cumulative dose (mg)	Fold increase per step
1	1	2.5	15	0.0015	0.0015	NA
2	1	5	15	0.0029	0.0044	2
3	1	10	15	0.0058	0.0102	2
4	1	20	15	0.0116	0.0218	2
5	2	5	15	0.029	0.0508	2.5
6	2	10	15	0.058	0.1088	2
7	2	20	15	0.116	0.2248	2
8	2	40	15	0.232	0.4568	2
9	3	10	15	0.5754	1.0322	2.48
10	3	20	15	1.1509	2.183	2
11	3	40	15	2.3017	4.4848	2
12	3	80	175	53.5152	58	2
Total time = 5.66 h						

NA, Not applicable/available.

were able to restart sorafenib using premedication and a 6-day oral tolerance protocol, with day 1 doses given every 15 minutes (Table LII, *A*). The patient developed erythema after the 11-step protocol, which was treated with 4 mg dimethindene maleate, with resolution. The patient was premedicated with methylprednisolone 24 mg on day 1, and premedicated with methylprednisolone 24 mg and fexofenadine 180 mg on days 2 to 12. Thereafter, fexofenadine was used only as needed.

More recently, Linauskiene et al[426] described a patient with sorafenib treatment complicated by fever and generalized urticaria 10 days into treatment. The urticaria resolved 5 days after discontinuation of sorafenib, systemic glucocorticoids, and oral antihistamines. The 8-day oral tolerance protocol (Table LII, *B*) was based on the Bauer et al[425] study, and was complicated by antihistamine-responsive pruritus during the first several days of the protocol.[426] This patient also developed facial urticaria after

TABLE XLIII. Desensitization protocol for pemetrexed

Step	Solution*	Infusion rate (mL/h)	Infusion time (min)
1	C	5	15
2	C	10	15
3	C	20	15
4	C	50	15
5	C	100	17.25
6	B	20	15
7	B	50	15
8	B	100	19.5
9	A	20	15
10	A	50	15
11	A	100	15
12	A	200	15.6

*Solution A: pemetrexed 815 mg + normal saline 100 mL; solution B: pemetrexed 40.75 mg + normal saline 50 mL; solution C: pemetrexed 4.075 mg + normal saline 50 mL.

TABLE XLIV. Rapid lenalidomide desensitization protocol

Time (min)	Dilution (mg/mL)	Volume (mL)
0	0.025 mg/mL	0.01
30		0.05
60		0.1
90		0.5
120		1
150		5
180		3.34
210	0.25 mg/mL	1
240		2
270		3
300		4
330	1.50 mg/mL	1
360		2
390		6

reaching the maintenance dose of 400 mg twice daily, which was managed with dose reduction to 400 mg in the morning and 200 mg in the evening. Premedication with prednisolone 30 mg and bilastine 20 mg was used on days 1 to 4, and premedication with bilastine 20 mg on days 5 to 7.

Sunitinib. Generalized hypersensitivity reactions are rare with sunitinib. Bar-Sela et al[427] described a patient presenting with onset of generalized acute urticaria and facial edema 4 days after starting sunitinib. The patient was desensitized 1 week after resolution of his symptoms, with oral premedications including prednisone 20 mg and promethazine 25 mg given 1 hour before initiation. Each of the 10 steps was carried out in 1-hour intervals, and he was observed overnight before discharge (Table LIII). The patient required desensitization with this protocol twice, because of a treatment pause. A mild pruritic rash developed after the first desensitization, but resolved with oral steroid and antihistamine, and he was able to continue the medication. The second desensitization was well tolerated, and he subsequently was continued on sunitinib treatment without hypersensitivity reactions.

Alectinib. In one report, a patient developed a skin rash affecting the arms and trunk starting 10 days after initiation of alectinib.[428] Skin biopsy was notable for perivascular infiltration of histiocytes, neutrophils, and lymphocytes in the upper dermis. The rash resolved completely after discontinuation of alectinib, and the patient underwent successful oral desensitization using a protocol that was administered over 9 days (Table LIV).

BIOLOGICALS

Rituximab (by Patrick Brennan, MD, and Meredith Dilley, MD)

General. Rituximab is a chimeric mouse-human mAb directed against CD20, an abundant surface receptor found on B lymphocytes. The incidence of clinically significant reactions to rituximab is very high, and varies widely with the indication for treatment. Most studies have reported reaction rates during the initial infusion ranging from 25% to more than 75%.[429-433] The incidence of reactions during subsequent infusions is much lower.[430,432] It should be noted, however, that severe infusion reactions can also occur only after several exposures, or on reexposure after a long hiatus. Most infusion reactions respond to symptomatic treatment and/or lowering of the infusion rate, and most reactions can be managed by the supervising oncologist or rheumatologist. Only a fraction of infusion reactions to rituximab warrant evaluation and treatment by an allergy specialist. Because of the high incidence of reactions, however, identifying cases that are appropriate for referral can be challenging. An allergist's evaluation is recommended for patients who have experienced reactions that are consistent with immediate-type hypersensitivity, severe reactions, repeated reactions, or progressive reactions with multiple medication administrations.

Major symptoms of hypersensitivity. Common infusion reactions can involve symptoms that are consistent with immediate-type hypersensitivity, including hypotension, bronchospasm, angioedema, urticaria, flushing, rhinitis, and pruritus. The use of rituximab for lymphoid malignancy also often precipitates malaise, fever, and chills, possibly secondary to tumor lysis. In autoimmune diseases, headache, nausea, and diarrhea have been commonly reported. The allergy specialist should also be aware of the possibility for serious, nonimmediate adverse reactions including serum sickness, SJS, TEN, myocardial infarction, arrhythmia, shock, and pulmonary toxicity.[434]

Diagnosis. Reactions to rituximab can be IgE-mediated. In patients with suspected rituximab hypersensitivity referred to an academic allergy practice, skin testing result for rituximab was reported as positive in 6 of 9 patients tested, suggesting that at least some reactions to rituximab may be IgE-mediated.[435] A case report has more thoroughly demonstrated the presence of anti-rituximab IgE in a patient who had experienced progressive hypersensitivity symptoms after rituximab exposure.[436] The use of a BAT has also been reported for reactions to rituximab, but further study is required before this modality can be used in clinical practice.[437] As a practical approach, skin testing to rituximab using 10 mg/mL epicutaneously, followed by 0.01 mg/mL, 0.1 mg/mL, and 1 mg/mL intradermally, is recommended. It should be noted that systematic testing of nonirritating concentrations for most mAbs has not been reported. A positive skin test result after a reaction consistent with immediate hypersensitivity should be interpreted as confirmation of allergy.

TABLE XLV. Slow desensitization to lenalidomide and schematic illustration of desensitization schedule*

Week†	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
1	2.5 mg						
2	2.5 mg			2.5 mg			2.5 mg
3		2.5 mg		2.5 mg		2.5 mg	2.5 mg
4	2.5 mg	2.5 mg	2.5 mg	5 mg	2.5 mg	5 mg	2.5 mg
5	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
6	10 mg	5 mg	10 mg	5 mg	10 mg	10 mg/d	

Step	Lenalidomide dose
1	2.5 mg PO during outpatient clinic visit and observation for 1 h. No further doses × 1 wk
2	2.5 mg PO every 3 d × 3 doses
3	2.5 mg PO every other day × 3 doses
4	2.5 mg PO qd × 3 doses
5	2.5 mg PO alternating with 5 mg PO × 6 doses
6	5 mg PO qd × 6 doses
7	5 mg PO alternating with 10 mg PO × 6 doses
8	10 mg/d*

PO, Per os (by mouth); *qd*, every day.
*This is an example using a target dose of 10 mg. Weekly complete blood cell counts with differential and liver function tests were obtained during desensitization.
†This regimen can be altered depending on the final target dose. For example, a target dose of 25 mg could be achieved by alternating the 10-mg dose with the 20-mg dose for a few doses, then introducing 25 mg/d. Once the patient has tolerated slow desensitization, repeat desensitization can be done over a 1-wk period, starting at 2.5 mg × 2 d, 5 mg × 2 d, 7.5 mg × 2 d, and then 10 mg/d.

TABLE XLVI. Thalidomide challenge protocol

Day	Time (h)	Dose (mg)
1	0	1
	0.5	2
	1	3
	1.5	4
Observation for 6 h		
2	0	25
	0.5	25
	1	50
Observation for 6 h		

However, a negative skin testing result should not dismiss the possibility of immediate hypersensitivity, because the sensitivity of this testing is not known. In addition, there may be non−IgE-mediated reactions to rituximab infusion that involve mast cell degranulation and mediators of allergic disease, and these reactions would also be amenable to the management approaches described herein. Therefore, a careful history of the reaction(s) experienced remains a valuable diagnostic tool.

Management. Although not standardized, both antihistamines and systemic glucocorticoids are routinely used as rituximab premedications for both oncologic and autoimmune indications. If a reaction occurs, the infusion should be stopped, and symptoms treated. For nonanaphylactic reactions, after symptoms have resolved, the infusion can generally be restarted at a slower rate. Because most infusion reactions occur during the first exposure and are not seen with subsequent exposures, standard reinfusion after a first-exposure infusion reaction is reasonable in the absence of a life-threatening reaction.

In a retrospective review of 67 patients who reacted to rituximab, 63% of reactions occurred during the first exposure; of these, 88% were grade 1 or 2.[438] Of these patients, 88% were rechallenged with rituximab on the same day, and those with a grade 1 reaction were able to complete the infusion. However, all 4 patients with a grade 3 reaction had a reaction during rechallenge. After a grade 2 reaction, 84% tolerated same-day challenge, but 5 patients had a subsequent mild reaction.

For patients referred for evaluation by an allergist, skin testing can be useful in guiding management.[439,440] If skin testing result is negative after a mild to moderate reaction that was consistent with immediate hypersensitivity, a graded dose challenge can be considered; 1/100 and 1/10 dose challenges before the full dose, with a 1-hour interval, are recommended. For patients with positive skin testing result, or for those with negative skin test results who experienced severe reactions consistent with immediate hypersensitivity, rapid desensitization to rituximab is recommended. Reinstituting treatment with mAbs is often urgent and time-sensitive, making the process of evaluation with skin testing difficult because of time limitations. When treatment options are limited, desensitization should be considered to allow for the continued use of these drugs in patients who have a reaction consistent with immediate hypersensitivity. Rapid desensitization has been a highly successful strategy for preventing immediate-type hypersensitivity reactions to rituximab and other mAbs.[440] In 2 case series of 14 and 7 adult patients with clinical histories consistent with rituximab hypersensitivity, all were successfully desensitized.[435,441] Successful desensitization has subsequently been reported with multiple protocols.[442] A 12-step protocol for desensitization of adults is recommended for the initial desensitization (Table LV).

Successful rapid desensitization to rituximab and other mAbs has also been reported in pediatric populations.[443-445] In a pediatric case series, rituximab desensitization was successfully used in 3 patients and a total of 17 infusions.[444] For an adolescent

TABLE XLVII. Thalidomide desensitization protocol

Day	Time (h)	Dose
1	0	0.1 μg
	0.5	0.2 μg
	1	0.3 μg
	1.5	0.4 μg
Observation for 1 h		
2	0	1 μg
	0.5	2 μg
	1	3 μg
	1.5	4 μg
Observation for 1 h		
3	0	0.1 mg
	0.5	0.2 mg
	1	0.3 mg
	1.5	0.4 mg
Observation for 1 h		
4	0	1 mg
	0.5	2 mg
	1	3 mg
	1.5	4 mg
	2	10 mg
	2.5	20 mg
	3	30 mg
	3.5	40 mg
Observation for 1 h		
5	0	100 mg
Observation for 1 h		

patient in this series, a similar 12-step protocol was used successfully (Table LVI). Two younger patients, however, experienced significant reactions when a 12-step protocol was used. For these patients, the desensitization protocol was successfully adapted to adjust for the patients' weight, with rate increases of not more than approximately 0.5 mg/kg/h, and with the final infusion rate not exceeding 2 mg/kg/h.

Cetuximab (by Timothy Kyin, MD)

Cetuximab is a chimeric mouse-human IgG_1 mAb against EGFR approved in 2005 for use in the United States for the treatment of metastatic colorectal cancer and squamous cell carcinoma of the head and neck. According to the product information, 3% of patients will experience a severe allergic reaction, with 90% of these reactions occurring on first exposure. Symptoms can include difficulty breathing, low blood pressure, shock, loss of consciousness, and/or heart attack.

Since its release, it has become evident that the rate of first-exposure hypersensitivity reaction is higher than previously described, with a regional preference for the southeastern United States. A 2007 review of patients receiving treatment with cetuximab at major centers in North Carolina and Tennessee showed that a grade 3 to 4 hypersensitivity reaction occurred in 19 (22%) of 88 patients.[446] Another multicenter study demonstrated that most patients who experienced a hypersensitivity reaction had preformed IgE to cetuximab without any previous exposure. The antibody was specific for galactose-α-1,3-galactose, which is present in the Fab portion of the cetuximab heavy chain.[447] Unlike most mAbs, cetuximab is generated in a mouse cell line (SP2/0), which expresses the gene for α-1,3-galactosyltransferase. Investigation of this regional variation in reaction rates led to the discovery that tick bites are the cause of IgE production to galactose-α-1,3-galactose.[448] This antibody has also been linked to delayed red meat anaphylaxis.[449] Some have suggested that evaluation of preexisting anticetuximab IgE could be used as a screening tool for pretreatment risk stratification.[450]

Current manufacturer guidelines recommend discontinuation of cetuximab after a severe allergic reaction, but there have been reports of successful desensitizations to this medication. The first such report was in 2009 in a 60-year-old woman with metastatic breast cancer who had hypotension, tachycardia, and oxygen desaturation after receiving only 28 mg of a planned 843-mg dose during her first exposure.[451] She was later found to have preexisting IgE to cetuximab. She was subsequently able to undergo a complete desensitization with a 5-bag, 20-step protocol. At Brigham and Women's Hospital, in conjunction with the Dana Farber Cancer Institute, a modified rapid desensitization has been used (unpublished data). This was in a 49-year-old woman with first-exposure hypersensitivity, involving urticaria, nausea, vomiting, and throat-closing sensation, and who had a positive intradermal skin test result at 1:10 dilution. A modified 1-bag, 5-step protocol with manipulation of the infusion rate was used for desensitization in this patient (Table LVII). Because of the proprietary nature of the cetuximab solution, there was concern about compound stability if the cetuximab was diluted with standard buffers. She has thus far completed 8 desensitizations of cetuximab with this protocol without complications.

Therefore, based on these experiences, it seems reasonable that desensitization is a viable option for this medication in the appropriate clinical setting.

Other mAbs (by Matthieu Picard, MD)

TNF-α inhibitors

General. TNF-α inhibitors are used for the treatment of inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, and psoriasis.[452-456] This class of biologics includes infliximab, certolizumab, adalimumab, golimumab, and etanercept.

Major symptoms of hypersensitivity. *Immediate hypersensitivity reactions to infliximab*: Immediate hypersensitivity reactions to infliximab occur in about 10% of patients and present with features that can suggest mast cell/basophil activation (flushing, pruritus, dyspnea, dizziness/hypotension) as well as with nonspecific symptoms (headache, increased blood pressure, chest and back pain, fever, and chills).[435,445,457-459] Immediate hypersensitivity reactions may occur with the first exposure but their incidence peaks around the seventh infusion.[435,457]

Injection-site reactions and systemic reactions to certolizumab, adalimumab, golimumab, and etanercept: Injection-site reactions occur in about 20% of patients treated with adalimumab or etanercept and in 2% to 6% of patients treated with certolizumab or golimumab.[460,461] Reactions to etanercept occur in median on the fourth injection, have their onset 1 to 2 days after injection, last 2 to 3 days, and may be accompanied by recall

TABLE XLVIII. Imatinib rapid oral desensitization*[421]

Step	Concentration	Volume (mL)	Dose (mg)
1	10 ng/mL	1, 2, 4	0.00007
2	100 ng/mL	1, 2, 4	0.00075
3	1 μg/mL	1, 2, 4	0.0075
4	10 μg/mL	1, 2, 4	0.075
5	100 μg/mL	1, 2, 4	0.75
6	1 mg/mL	1, 2, 4	7.5
7	10 mg/mL	1, 2, 4	75
8	100-mg tablet	1	100
9	100-mg tablet × 2	2	200

*Each step was administered sequentially in 15-min intervals to the 200-mg dose. An additional 100 mg was given at home the evening after desensitization, and the maintenance dose of 400 mg daily was started the next morning.

TABLE XLIX. Imatinib slow oral desensitization*[422]

Day	Concentration	Volume (mL)	Daily dose (mg)
1	1 mg/mL	1, 2, 4	7
2-4	10 mg/mL	1, 2, 4	70
5-7	100-mg tablet	1 tablet	100
8	100-mg tablet	1 tablet	107
	1 mg/mL	1, 2, 4	
9-11	100-mg tablet	1 tablet	170
	10 mg/mL	1, 2, 4	
12-14	100-mg tablet	2 tablets	200
15	100-mg tablet	2 tablets	270
	10 mg/mL	1, 2, 4	
16-21	100-mg tablet	3 tablets	300
22	100-mg tablet	3 tablets	370
	10 mg/mL	1, 2, 4	
23	100-mg tablet	4 tablets	400

*Daily doses were administered once daily. When multiple doses were administered on the same day, each step was administered in 20-min intervals.

TABLE L. Crizotinib rapid oral desensitization*[423]

Step	Dose (mg)
1	10
2	15
3	25
4	50
5	100

*Each step was administered sequentially in 30-min intervals.

reactions (local reactions at the site of previous injections).[461] These reactions usually wane over time.[461] Systemic reactions have rarely been reported with TNF-α inhibitors that are administered subcutaneously.[462]

Nonimmediate hypersensitivity reactions: Serum sickness–like reactions have been described with infliximab and adalimumab although they are much less frequent than immediate hypersensitivity reactions.[460] Onset is typically from 5 to 7 days after infusion, and the hypersensitivity reaction may involve fever, malaise, arthralgia/arthritis, and an erythematous (sometimes) urticarial skin eruption.[463] Psoriasiform and eczematous skin eruptions may develop during treatment with TNF-α inhibitors.[464] Other rare reactions that may occur include symmetrical drug-related intertriginous and flexural exanthem, erythema multiforme, SJS, and various autoimmune diseases such as drug-induced lupus.[465-468]

Diagnosis. IgE-mediated reactions account for a subset of immediate hypersensitivity reactions to infliximab and may be the cause of some injection-site reactions and also of rare systemic reactions to adalimumab and etanercept.[445,462] A positive immediate skin test response to infliximab and anti-infliximab IgEs were seen on average in 28% (range, 4%-67%) and 21% (range, 13%-27%) of reactive patients, respectively.[435,445,469-471] Suggested skin testing concentrations for the various TNF-α inhibitors are presented in Table LVIII. In patients with a negative skin test result, an IgG-mediated mechanism may be responsible for the hypersensitivity reaction. Patients with anti-infliximab IgGs are at increased risk (relative risk varies from 2.4 to 4.0) of immediate hypersensitivity reactions compared with patients without such antibodies.[472,473]

TABLE LI. Crizotinib rapid oral desensitization*[424]

Step	Concentration (mg/mL)	Volume (mL)	Dose (mg)
1	0.05	1.25	0.0625
2	0.05	2.5	0.125
3	0.5	0.5	0.25
4	0.5	1	0.5
5	0.5	2	1
6	5	0.4	2
7	5	0.8	4
8	5	1.6	8
9	5	3.2	16
10	5	6.25	31.25
11	5	12.5	62.5
12	5	25	125

*Each step was administered sequentially in 15-min intervals.

Management. When treatment is indicated, patients with an immediate hypersensitivity reaction to infliximab should preferably be reexposed through desensitization (Table LIX) if skin testing result is positive or the initial hypersensitivity reaction was severe or they experienced recurrent hypersensitivity reactions despite added premedication and/or a slowed infusion rate.[435,459,469,470,474] In others, re-treatment using the protocols developed by Cheifetz et al can be used and appear to be safe.[459,469,475] These protocols vary depending on the severity of the initial reaction and consist of slowly increasing the infusion rate after administering premedication (H_1 antihistamine, acetaminophen, and corticosteroids for severe reactions) (Figure 5). The risk of a recurrent reaction with subsequent exposures is around 33% on the first reexposure and progressively decreases thereafter.[475] Therefore, in patients who tolerate desensitization well, it may be reasonable to progressively shorten desensitization protocols and eventually proceed to a challenge procedure except in those with an IgE-mediated allergy (Figure 6).[476]

Anti-infliximab antibodies do not cross-react with adalimumab.[477] However, patients who develop anti-infliximab antibodies are more prone to develop antiadalimumab antibodies and have a higher treatment failure rate with adalimumab.[461] Also, rare cases of patients with immediate hypersensitivity reaction to infliximab have been described who also reacted to adalimumab (injection-site reaction or serum sickness—like reactions).[469,478] Despite these caveats, switching to adalimumab after a hypersensitivity reaction to infliximab can be attempted.[459,469]

Injections-site reactions to etanercept, adalimumab, golimumab, or certolizumab are usually treated with ice, an oral antihistamine, topical corticosteroids, and analgesics.[460] Desensitization could be considered for those with important injection-site reactions or with systemic reactions (Table LX).[462]

Desensitization is not a safe method of preventing nonimmediate hypersensitivity reactions to TNF-α inhibitors, but the optimal approach remains unclear. Switching to another TNF-α inhibitor has not been adequately studied, though some authors have reported that reexposure to the suspected culprit drug may not necessarily lead to a recurrent reaction.[465,479]

Ofatumumab and obinutuzumab. Ofatumumab and obinutuzumab target CD20 and are used in the treatment of B-cell malignancies.[480-482] Immediate hypersensitivity reactions, thought to be caused by a cytokine release syndrome, occur in more than 50% of patients treated with 1 of these mAbs on first exposure.[481,483,484] Although the incidence of hypersensitivity reactions rapidly decreases with subsequent infusions, severe reactions that led to drug discontinuation and even fatal hypersensitivity reactions, in the case of ofatumumab, have been reported.[481,483,485] Skin testing to these mAbs has not been studied. The approach used for hypersensitivity reactions to rituximab can be applied to these agents because at least 2 patients were successfully desensitized to obinutuzumab (Figure 6).[474,476]

Brentuximab vedotin. Brentuximab vedotin is a chimeric mAb coupled with a microtubule-disrupting agent used in the treatment of $CD30^+$ lymphomas.[486] Several cases of anaphylaxis have been reported, which usually occurred after at least 1 uneventful exposure.[487-489] Skin testing to brentuximab vedotin could help identify patients with an IgE-mediated allergy.[474] Desensitization appears to be the method of choice for reexposure in patients with anaphylaxis (Table LIX) (Figure 6).[474,487-489]

Trastuzumab. Trastuzumab is a humanized mAb against the human EGFR 2 used in the treatment of breast cancer.[490] Sixteen percent to 40% of patients experience an immediate hypersensitivity reaction during their first exposure to trastuzumab, with clinical features suggestive of a cytokine release syndrome.[491,492] Most of these patients tolerate future infusions after premedication with an antihistamine and a corticosteroid.[490-492] Patients who experience an immediate hypersensitivity reaction after tolerating several infusions of trastuzumab are likely to have developed an IgE-mediated reaction to the mAb. Skin testing (Table LVIII) can be useful to identify those patients.[435,470] Although most patients with a mild to moderate hypersensitivity reaction due to cytokine release will tolerate reexposure through a standard reinfusion, desensitization (Table LIX) should be considered for those with a severe cytokine release reaction or with an IgE-mediated reaction (Figure 6).[435,470,474,491,492] Papulopustular acneiform skin eruptions have been reported in some patients treated with trastuzumab. All were able to continue treatment with trastuzumab and responded well to acne treatment.[493]

Pertuzumab. Pertuzumab is a humanized mAb that, compared with trastuzumab, recognizes a different epitope of human EGFR 2.[494] These 2 mAbs are used in combination in the treatment of breast cancer.[494-496] Very few patients experience immediate hypersensitivity reactions to pertuzumab.[495] However, in a recent case report, a patient with anaphylaxis on second exposure to pertuzumab was successfully reexposed through desensitization.[497] Skin testing result to pertuzumab was negative (Table LVIII), but a BAT result was positive, suggesting an IgE-mediated mechanism.[497] Therefore, desensitization (Table LIX) could be considered for patients with suspected IgE-mediated reactions to this mAb even in the absence of a positive skin test result (Figure 6).[474,476]

Bevacizumab. Bevacizumab is a humanized mAb used in the treatment of many types of cancer that targets vascular endothelial growth factor.[498] Immediate hypersensitivity reactions to bevacizumab occur in less than 3% of patients and are usually mild.[499] Of the rare patients with an immediate hypersensitivity reaction, most tolerate subsequent exposures with premedication

TABLE LII. Sorafenib oral tolerance induction

Day	Step	Dose (mg)	Intervals
A[425]			
1	1	0.4	Every 15 min
	2	0.8	
	3	1.6	
	4	3.2	
	5	6	
	6	12	
	7	24	
	8	50	
	9	100	
	10	200	
	11	400	
2	1	100 mg	Every 2 h
	2	100 mg	
	3	200 mg	
	4	200 mg	
3-5	1	200 mg	Every 2 h
	2	200 mg	
	3	200 mg	
	4	200 mg	
6 and onwards	1	400 mg	Every 12 h
	2	400 mg	
B[426]			
1	1	0.4	Every 15 min
	2	0.8	
	3	1.6	
	4	3.2	
	5	6	
	6	12	
	7	24	
	8	50	
	9	100	
	10	200	
	11	400	
2	1	100 mg	
	2	100 mg	3 h later
	3	200 mg	2 h later
3	1	100 mg	Every 2 h
	2	200 mg	
	3	200 mg	
4	1	200 mg	Every 2 h
	2	200 mg	
	3	200 mg	
5-7	1	200 mg	Every 2 h
	2	200 mg	
	3	200 mg	
	4	200 mg	
8 and onwards	1	400 mg	Every 12 h
	2	400 mg	

with an antihistamine and a reduction in the infusion rate.[500] However, in 2 recent studies, two-thirds of patients with an immediate hypersensitivity reaction to bevacizumab had a positive skin test result (Table LVIII) and all underwent successful desensitization (Table LIX).[470,474] Therefore, an IgE-mediated mechanism should be suspected in those with recurrent hypersensitivity reactions or with a severe immediate hypersensitivity reaction (Figure 6).[474,476]

Tocilizumab. Tocilizumab is a humanized mAb that binds to IL-6 receptors to block IL-6 signaling.[501] It is used to treat rheumatoid arthritis and systemic or polyarticular juvenile arthritis.[501] Immediate hypersensitivity reactions to tocilizumab are rare, but several cases of anaphylaxis have been reported occurring from the second exposure onward.[502,503] Skin testing (Table LVIII) is usually useful in identifying patients with an IgE-mediated hypersensitivity reaction, and desensitization (Table LIX) should be considered the method of choice to reexpose those patients to tocilizumab (Figure 6).[470,474,502,503]

Omalizumab. Omalizumab is a humanized mAb that binds free IgE antibodies.[504] It is administered subcutaneously and is used in the treatment of moderate to severe allergic asthma and chronic idiopathic urticaria.[504] Anaphylaxis to omalizumab is rare and is estimated to occur in 0.1% to 0.2% of patients.[505] A history of anaphylaxis, regardless of the cause, was recently shown to increase the risk of developing anaphylaxis to omalizumab to 0.6%.[506] More than half the cases of anaphylaxis to omalizumab occur less than 1 hour after medication administration. However, delayed reactions (>24 hours after the injection) and a protracted course, with symptoms progressively developing over the course of several hours, have been reported.[506,507] Two patients with symptom onset more than 24 hours after the injection were rechallenged and both had recurrent reactions, strengthening the causality of omalizumab in these reactions.[507] The mechanism of immediate hypersensitivity reactions to omalizumab remains elusive. Skin prick testing protocols with full-strength concentration followed by intradermal testing with 1:10,000 dilution have been reported.[508] Serum tryptase was normal in all patients with anaphylaxis to omalizumab in whom it was measured.[509,510] Specific IgE or IgG against omalizumab were not detected in 21 cases of anaphylaxis.[507] Skin testing result to nonirritating concentrations of omalizumab was negative in all patients tested (Table LVIII).[506] For patients with hypersensitivity reactions to omalizumab, the approach remains uncertain, but rechallenge is not recommended especially in patients with severe reactions.[476] Desensitization (Tables LXI and LXII) may be attempted, followed by weekly or biweekly administration to preserve the desensitized state and may allow for continued administration in some patients.[474,511]

Insulin (by Christina Yee, MD, PhD)

General. Adverse reactions to insulin have decreased in frequency since the introduction of synthetic recombinant DNA human insulin analogues, but recombinant humanized insulin can still be associated with hypersensitivity reactions. Prevalence of suspected insulin allergy has been reported in as few than 3% of patients annually.[512] Pediatric and adult patients with either type 1 or type 2 diabetes may be affected.

Recombinant human insulin analogues such as lispro, aspart, and glulisine (short-acting) or detemir and glargine (long-acting) have decreased immunogenicity compared with bovine or porcine

TABLE LIII. Sunitinib rapid oral desensitization*[427]

Step	Concentration (mg/mL)	Volume (mL)	Dose (mg)
1	0.2	0.25	0.05
2	0.2	0.5	0.1
3	0.2	1	0.2
4	0.2	2.5	0.5
5	1	1	1
6	1	2	2
7	1	4	4
8	1	8	8
9	16-mg capsule	1 capsule	16
10	25-mg capsule	1 capsule	25

*Each step was administered sequentially in 60-min intervals.

TABLE LIV. Alectinib slow oral desensitization*[428]

Day	Dose (mg)
1, 2	40
3, 4	80
5, 6	160
7, 8	300
9	Twice-daily 300

*Each step was administered daily, with the exception of day 9 and on.

TABLE LV. Rituximab desensitization protocol (1000 mg)*

Solution 1	250 mL of	0.040 mg/mL
Solution 2	250 mL of	0.400 mg/mL
Solution 3	250 mL of	3.969 mg/mL

Step	Solution	Rate (ml/h)	Time (min)	Volume infused per step (mL)	Dose administered with this step (mg)	Cumulative dose (mg)
1	1	2.0	15	0.50	0.02	0.02
2	1	5.0	15	1.25	0.05	0.07
3	1	10.0	15	2.50	0.10	0.17
4	1	20.0	15	5.00	0.20	0.37
5	2	5.0	15	1.25	0.50	0.87
6	2	10.0	15	2.50	1.00	1.87
7	2	20.0	15	5.00	2.00	3.87
8	2	40.0	15	10.00	4.00	7.87
9	3	10.0	15	2.50	9.92	17.79
10	3	20.0	15	5.00	19.84	37.63
11	3	40.0	15	10.00	39.69	77.32
12	3	80.0	175	232.50	922.68	1000.00

*Total time 5 h 40 min.

insulin preparations. Short-acting insulin preparations are believed to be the least frequently associated with sensitivity because the rapidity of absorption is thought to decrease immune exposure. Allergic sensitization may also occur because of insulin additives or materials used to administer insulin injections or infusions.

Insulin reactions can pose significant challenges for diabetic patients, who may have no alternatives to lifelong insulin therapy.

Major symptoms of hypersensitivity. Adverse reactions to insulin may present as immediate-type (IgE-mediated) hypersensitivity, delayed-type hypersensitivity, serum sickness, or other reactions.

Immediate-type hypersensitivity reactions (type I, or IgE-mediated) are the most commonly reported insulin reactions. The causative antigen may be the insulin itself or other components of the preparation. Symptoms may encompass the full

TABLE LVI. Rituximab desensitization protocol for pediatric patients*[444]

Solution	Total volume (mL)	Drug per bag (mg)	Concentration (mg/mL)
1	250	2.06	0.008
2	250	20.6	0.082
3	250	205.189	0.821

Step	Solution	Rate(mL/h)	Rate (mg/kg/h)	Time (min)	Dose per step (mg)	Cumulative dose (mg)
1	1	1	0.0006	15	0.0021	0.0021
2	1	2.5	0.002	15	0.0052	0.0072
3	1	5	0.003	15	0.0103	0.0175
4	1	10	0.006	15	0.0206	0.0381
5	2	2.5	0.02	15	0.0515	0.0896
6	2	5	0.03	15	0.103	0.1926
7	2	10	0.07	15	0.206	0.3986
8	2	20	0.1	15	0.412	0.8106
9	3	5	0.3	15	1.0259	1.8366
10	3	10	0.7	15	2.0519	3.8885
11	3	20	1.3	15	4.1038	7.9922
12	3	30	2	482.5	198.0078	206

*Total infusion time: 648 min; final infusion rate: 2.0 mg/kg/h.

TABLE LVII. Cetuximab desensitization protocol: 1-solution, 5-step protocol*

Step	Solution	Rate (mL/h)	Time (min)	Volume infused per step (mL)	Dose administered with this step (mg)	Cumulative dose (mg)
1	1†	5.0	30	2.50	5.0658	5.0658
2		10.0	30	5.00	10.1316	15.1974
3		20.0	30	10.00	20.2632	35.4606
4		40.0	30	20.00	40.5264	75.9870
5		80.0	256.87	342.49	694.0011	769.9881

*Target dose: 770.0 mg; volume per bag: 380 mL; final rate of infusion: 80 mL/h; calculated final concentration: 2.026 mg/mL; total time: 376.87 min (6.28 h).
†Solution 1: 380 mL of 2.026 mg/mL (total per bag: 770.002 mg).

spectrum of immediate-type reactions, from mild pruritus or rash to generalized urticaria or to dyspnea, hypotension, or other symptoms of anaphylaxis. Localized symptoms may be most prominent near the site of the insulin injection or infusion. Systemic reactions are rare, but anaphylaxis to insulin has been reported even with recombinant insulin preparations.[513-515] Immediate-type insulin allergy frequently occurs within several weeks after initiation of insulin therapy or after restarting therapy, but it can also develop after years of treatment.

Symptoms of insulin reactions may also be delayed in presentation. In the case of immune complex—mediated (type III) reactions, subcutaneous nodules may develop at the injection site after 2 to 6 hours, with later symptoms of serum sickness including pruritic rash, joint pains, fatigue, and elevated inflammatory markers.[516] Delayed-type hypersensitivity (type IV) reactions to insulin detemir have also been reported, with symptoms of prolonged induration, pain, warmth, and swelling at the injection site, or, in 1 case report, leukoclastic vasculitis.[517,518] Delayed-type hypersensitivity reactions may also occur in response to components of insulin preparations, such as protamine or metacresol or from components of equipment used for insulin administration, such as adhesives or tubing.[519,520]

Insulin resistance and lipoatrophy at injection sites were reported in patients receiving bovine or porcine insulin, and were linked to circulating antibodies to insulin.[521] Transition to recombinant human insulins has eliminated many impurities associated with animal insulin preparations, and such associated side effects are now rare.

Diagnosis. A careful history is vital in the evaluation for a potential insulin reaction. Other causes of symptoms must be excluded. In a retrospective study, 59% of suspected cases of insulin "allergy" did not have an allergic cause.[522] Patients with diabetes mellitus have increased incidence of other autoimmune diseases, which should also be considered on the differential diagnosis. Chronic urticaria, atopic dermatitis, psoriasis, vasculitis, and other systemic autoimmune diseases may present with rash or other skin manifestations.

Timing and characteristics of associated symptoms should be considered to determine the likely type of reaction. Allergic reactions to insulin can occur to the insulin itself; to preservatives and solvents such as metacresol, phenol, or sodium phosphate; or to insulin additives such as protamine or zinc, which help slow insulin absorption.[523-526] In addition, hypersensitivity reactions have been reported to injection or infusion pump equipment, latex, nickel, epoxy resin, and local disinfectants.[527,528] Therefore, consideration must also be given to components of the insulin preparation being used, as well as to components of equipment used for infusion (syringes, needles, infusion pump tubing, adhesives, etc), latex in this equipment or in the stopper of insulin vials, and possible reactions to alcohol or disinfectant wipes.

TABLE LVIII. Suggested skin testing concentrations for mAbs*

Agent	SPT	IDT
Adalimumab†‡[462]	40 mg/mL (full strength)	0.4 mg/mL (1/100 dilution)
Bevacizumab†[380,470]	25 mg/mL (full strength)	2.5 mg/mL (1/10 dilution)‡
Brentuximab vedotin[474]	1.8 mg/mL	0.18 mg/mL
Certolizumab	NA	NA
Cetuximab†‡[380,470]	2 mg/mL (full strength)	0.2 mg/mL (1/10 dilution)§
Etanercept†‡[462]	50 mg/mL (full strength)	0.5 mg/mL (1/100 dilution)
Golimumab	NA	NA
Infliximab†[380,445]	10 mg/mL (full strength)	1 mg/mL (1/10 dilution)
Obinutuzumab	NA	NA
Ofatumumab	NA	NA
Omalizumab†[508]	125 mg/mL (full strength)‖	0.00125 mg/mL (1/100,000 dilution)
Pertuzumab[497]	1.6 mg/mL (≈1/20)¶	0.16 mg/mL (≈1/200 dilution)§
Rituximab†[380,435]	10 mg/mL (full strength)	1 mg/mL (1/10 dilution)#
Tocilizumab†[502]	20 mg/mL (full strength)	20 mg/mL (full strength)
Trastuzumab[435]	21 mg/mL (full strength)	2.1 mg/mL (1/10 dilution)

NA, Not available.
*All dilutions should be made in normal saline (from Picard et al).[476]
†Concentrations shown to be nonirritating by testing on healthy control subjects.
‡A concentration of 25 mg/mL was also shown to be nonirritating.[380]
§A concentration of 0.5 mg/mL was shown to be nonirritating in 8 controls, and another group reported a concentration of 5 mg/mL to be nonirritating.[380,450]
‖Omalizumab should be reconstituted with normal saline to avoid false-positive results.[508]
¶Full-strength concentration is 30 mg/mL. Pertuzumab was tested on only 1 reactive subject, with negative results at 1.6 mg/mL (SPT) and up to 0.16 mg/mL (IDT). Higher concentrations could be nonirritating.
#Although 1 mg/mL (IDT) is more commonly used, a maximal concentration of 10 mg/mL (full strength) for rituximab IDT is recommended by the European Network on Drug Allergies and does not seem irritating.[380]

Although diagnostic testing for anti-insulin IgE and IgG_4 antibodies has been studied, the presence of insulin-specific antibodies cannot be used to establish a diagnosis of insulin allergy, because anti-insulin IgE antibodies can be present in patients with no apparent allergy.[529] BATs have also been used to measure *in vitro* responses to insulin, but their clinical utility has not been established, and the tests are not commercially available.

Skin testing for the insulin preparations used, alternative insulin preparations, and additives may help distinguish the specific allergenic component or components (Table LXIII). Skin testing for short-acting insulins (Table LXIV), which may be less allergenic, may be considered for patients with possible allergic symptoms to continuous subcutaneous insulin infusion, or patients with allergy to other forms of insulin for whom this therapy may be considered.

Positive insulin skin testing results have been reported in patients receiving insulin without allergic symptoms, so skin test results must be correlated with clinical symptoms.[522] It may be helpful to include alternative insulin preparations in skin testing, to identify preparations to which a patient may not be sensitized. Testing should also include additives present in each formulation of interest. Sterile diluent vials (eg, Lily Sterile Diluent 1-ND 800) are commonly used for injection teaching and diluting insulin. These contain additives such as metacresol and glycerin at concentrations equivalent to insulin preparations, so they may be helpful in skin testing.

In the case of a suspected reaction to a long-acting insulin preparation containing protamine, sensitization to protamine should also be excluded. Testing result should be interpreted with care, because a significant percentage of diabetic patients who have received neutral protamine Hagedorn insulin without history of adverse reaction may have positive skin testing result and/or serum-specific IgE to protamine.[530,531] Skin prick testing for protamine may be performed at a dilution matching the approximate concentrations contained in neutral protamine Hagedorn insulin (350 μg/mL, a 30-fold dilution of stock protamine, 10 mg/mL).[532]

If the insulin preparation has a stopper containing latex, skin and/or blood testing for latex allergy may also be included in the evaluation. However, many preparations of insulin are now latex-free.

Serum sickness–type reactions to insulin are relatively rare, and have been diagnosed primarily on the basis of clinical symptoms. Skin biopsy has shown perivascular lymphocytic infiltrate in some cases.[518] For evaluation of delayed-type hypersensitivity to insulin, intradermal skin testing result to insulin has been reported to be positive in some patients after 24 or 48 hours.[522,532] Patch testing can also been performed for potential contact dermatitis reactions to nickel in subcutaneous infusion needles, acrylates in infusion catheters, adhesives in butterfly catheters, or other additives such as parabens, phenol, and isophane.

If timing and location of symptoms are insufficient to establish the diagnosis, skin biopsy may be helpful to rule out systemic dermatologic conditions such as vasculitis, psoriasis, or eczema.

Management. Initial management of suspected allergic reactions to insulin may include antihistamines and/corticosteroids, particularly for local reactions.

Changing therapy may be considered. Patients with type 2 diabetes and insulin allergy can have a trial of conventional oral hypoglycemic medications. Liraglutide, a glucagon-like peptide-1 receptor agonist that promotes endogenous insulin secretion, has also been used in insulin allergy.[533]

TABLE LIX. Example of a 3-bag/12-step desensitization protocol that is applicable for most mAbs administered intravenously

Rituximab desensitization protocol (1000 mg)						
Solution 1				250 mL of		0.040 mg/mL
Solution 2				250 mL of		0.400 mg/mL
Solution 3				250 mL of		3.969 mg/mL
Step	**Solution**	**Rate (mL/h)**	**Time (min)**	**Volume infused per step (mL)**	**Dose administered with this step (mg)**	**Cumulative dose (mg)**
1	1	2.0	15	0.50	0.02	0.02
2	1	5.0	15	1.25	0.05	0.07
3	1	10.0	15	2.50	0.10	0.17
4	1	20.0	15	5.00	0.20	0.37
5	2	5.0	15	1.25	0.50	0.87
6	2	10.0	15	2.50	1.00	1.87
7	2	20.0	15	5.00	2.00	3.87
8	2	40.0	15	10.00	4.00	7.87
9	3	10.0	15	2.50	9.92	17.79
10	3	20.0	15	5.00	19.84	37.63
11	3	40.0	15	10.00	39.69	77.32
12	3	80.0	175	232.50	922.68	1000.00
Total time 5 h 40 min						

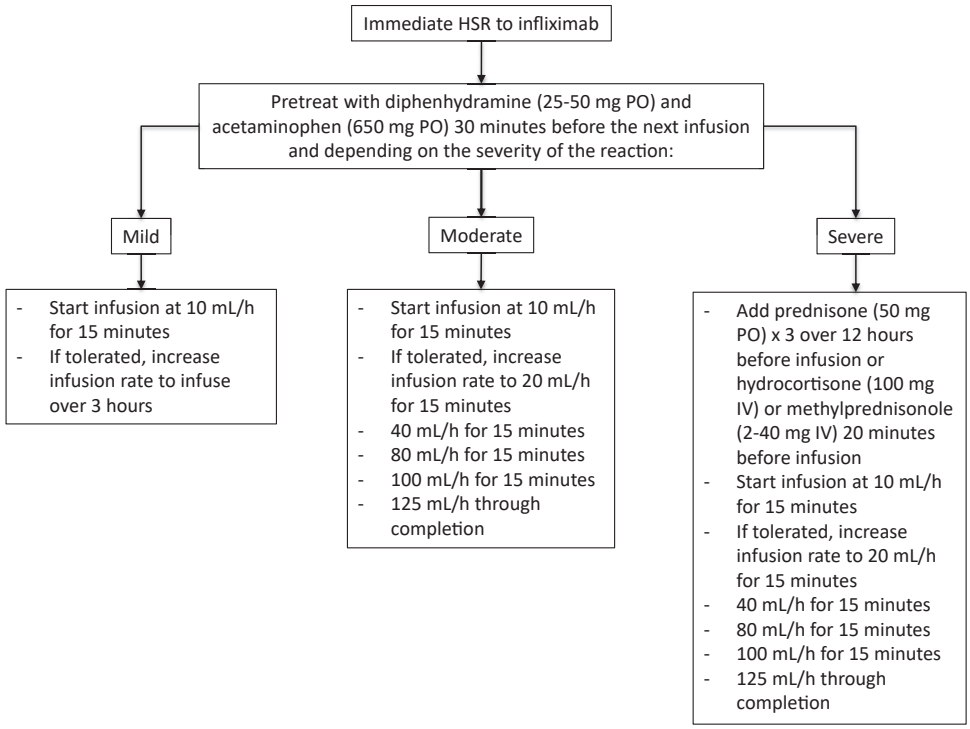

FIGURE 5. Protocol for desensitization to infliximab.[475] *IV,* Intravenous; *PO, per os* (by mouth).

If ongoing insulin therapy is required, changing to an alternative insulin preparation may be sufficient to avoid further symptoms. In the case of immediate-type reactions, if switching insulin preparations is not feasible or alternative therapies do not adequately control blood sugar levels, immunotherapy in the form of desensitization may be considered. Established desensitization protocols may administer insulin as increasing increments of subcutaneous doses, continuous subcutaneous infusions delivered by insulin pumps, or (rarely) by intravenous infusion, with either regular insulin forms or recombinant insulin.[534-537] Insulin desensitization has been performed starting with subcutaneous infusion at 1×10^{-3} units and doubling every 15 to 20 minutes, up to a dose of 1 unit, then switching to continuous infusion through the insulin pump to maintain desensitization. Transition from regular insulin to longer-acting forms of insulin can also be attempted in desensitization (Table LXV). Depending on patient size and total dose of insulin, blood glucose levels may be monitored before, after, and

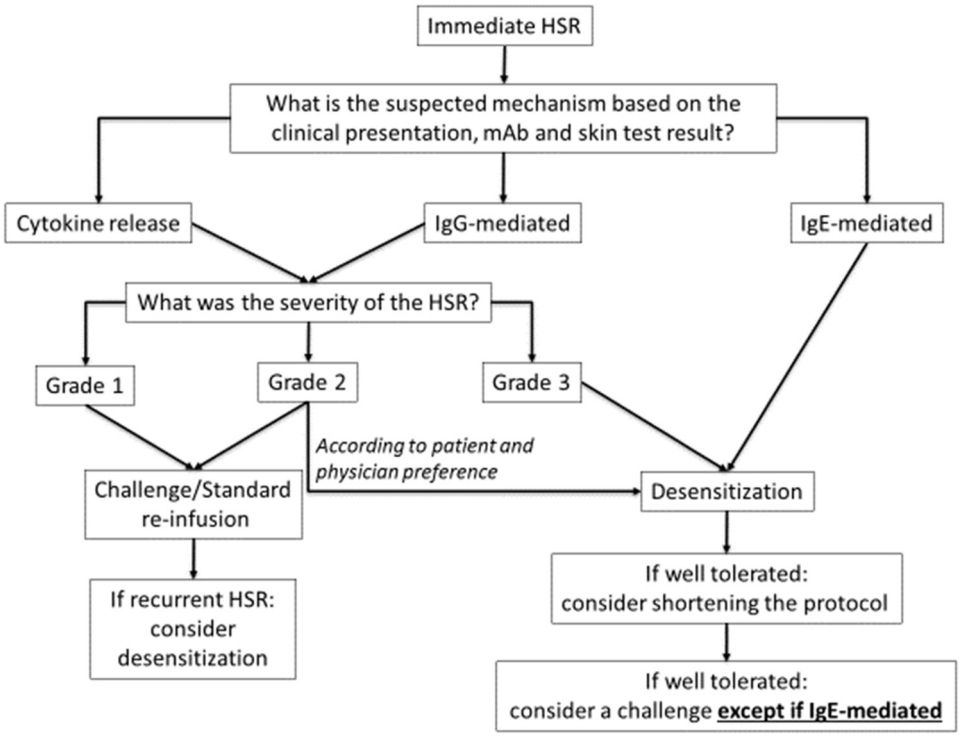

FIGURE 6. Suggested algorithm for the management of immediate hypersensitivity reactions to mAbs. Reactions due to cytokine release syndrome typically occur on the first administration and wane rapidly with subsequent exposures. Symptoms usually include fever, chills, rigors, and dyspnea but flushing, dizziness/hypotension, and gastrointestinal symptoms can also be seen. IgE-mediated and IgG-mediated reactions generally occur after at least 1 uneventful administration although IgE-mediated reactions have been described on first exposure to cetuximab due to preformed IgEs. IgG-mediated reactions have not been clearly demonstrated in humans, but they could account for reactions similar to IgE-mediated hypersensitivity reactions but in which IgE antibodies cannot be demonstrated (eg, skin testing result is negative). Grade 1 immediate hypersensitivity reactions present with symptoms that are limited to the skin (eg, flushing) or that involve a single organ/system and that are mild (eg, mild back pain). Grade 2 hypersensitivity reactions present with symptoms that involve at least 2 organs/systems (eg, flushing and dyspnea) but without a significant drop in blood pressure or in oxygen saturation. Grade 3 hypersensitivity reactions present with symptoms that typically involve at least 2 organs/systems and with a significant drop in blood pressure (systolic $\leq$ 90 mm Hg and/or syncope) and/or in oxygen saturation ($\leq$92%). Modified with permission from Picard et al.[476]

during the desensitization. For severe or refractory cases, desensitization has been combined with systemic cortisosteroids or other immune modulators such as prednisolone, rituximab, omalizumab, or mycophenolate.[538]

Delayed reactions at the injection site may be of either type III or type IV, and skin patch testing result may be negative. Large local reactions may respond to antihistamines or, if needed, local injections of steroids (100 mg dexamethasone diluted in 100 units insulin and used for subcutaneous injections or continuous infusion with insulin pump). Topical cromolyn sodium may also be compounded as a lotion or cream for local application. If local injections are not sufficient to control symptoms, desensitization can also be attempted. For treatment of delayed reactions, change in insulin preparations may also be beneficial. For type III reactions, successful treatment with MTX,[518] colchicine, and 6-mercaptopurine (6-MP),[539] as well as plasmapheresis,[540] have been reported.

Conclusions. Insulin allergy is a rare, but serious condition. Patients may be sensitized to insulin itself, to additives in insulin preparations, or to equipment used to administer subcutaneous doses. Evaluation begins with a history and close examination of additives contained in the form of insulin administered (Table LXIII). Skin testing with insulin and additives may be helpful to evaluate immediate-type reactions, and patch testing may be useful for delayed reactions. The first steps in management are to identify potential alternative insulin forms and treat symptoms with antihistamine and steroids if indicated. Large local reactions may benefit from local steroid injection and topical cromolyn preparation, and may improve over time. If initial strategies are not successful in preventing reactions, subcutaneous desensitization may be attempted.

Progestogens including progesterone (by Dinah Foer, MD, Andrew MacGinnitie, MD, PhD, and Kathleen M. Buchheit, MD)

General. Progesterone is an endogenous steroid hormone involved in the menstrual cycle and pregnancy. Synthetic progesterone preparations known as progestins are also used as contraception and hormone replacement, particularly in the setting of *in vitro* fertilization. Adverse reactions to both endogenous progesterone and exogenous progestins have been documented and were initially termed autoimmune progesterone

TABLE LX. Desensitization protocol for etanercept and adalimumab*

Time (min)	Dose (mg)	Dilution	Volume administered (mL)
Etanercept			
Day 1			
0	0.25	1/100	1
30	0.5	1/10	0.2
60	1	1/10	0.4
90	2	1/10	0.8
120	4	Undiluted	0.16
150	4.5	Undiluted	0.18
Day 2			
0	0.25	1/100	1
30	0.5	1/10	0.2
60	1	1/10	0.4
90	2	1/10	0.8
120	4	Undiluted	0.16
150	4.5	Undiluted	0.18
Day 3			
0	0.5	1/100	1
30	1	1/10	0.2
60	2	1/10	0.4
90	4	1/10	0.8
120	8	Undiluted	0.16
150	16	Undiluted	0.32
180	18.5	Undiluted	0.37
Adalimumab			
0	0.5	1/100	1
30	0.75	1/10	0.15
60	1.25	1/10	0.25
90	2.5	1/10	0.5
120	5	Undiluted	0.1
150	10	Undiluted	0.2
180	20	Undiluted	0.4

*Once desensitization was achieved, patients were administered the mAb weekly to maintain desensitization (adapted from Bavbek et al[462]).

TABLE LXI. Desensitization protocol for omalizumab*

Time (min)	Dose (mg)	Dilution	Volume administered (mL)
0	0.0625	1/100	0.05
30	0.625	1/100	0.5
60	1.25	1/10	0.1
90	2.5	1/10	0.2
120	5	1/10	0.4
150	10	1/10	0.8
180	20	Undiluted	0.16
210	37-40†	Undiluted	0.30-0.32
240	37-55†	Undiluted	0.30-0.44
270	37-55†	Undiluted	0.30-0.44

*The dose of omalizumab to which patients were desensitized was lower than their target dose and subsequent injections were administered weekly or biweekly.
†Depending on the total dose to be administered.

dermatitis, but more recently, the terminology has been changed to progestogen hypersensitivity (PH) to more accurately reflect the pathobiology.[541,542] Hypersensitivity reactions to progesterone are rare, with just over 100 cases reported, but with the increased use of exogenous progestogens, PH has become more frequently described.[543]

Clinical presentation. Onset of symptoms can occur in women any time between menarche and menopause. Endogenously triggered presentations are often cyclical, because progesterone levels peak approximately 1 week before the onset of menses.[544] In cases of PH associated with exogenous progesterone, the timing of symptoms should correlate with progestin

TABLE LXII. Desensitization protocol for omalizumab (target dose = 150 mg)*

Time (min)	Dose (mg)	Dilution	Volume administered (mL)
0	1.5	12.5 mg/mL	0.12
30	3	12.5 mg/mL	0.24
60	6	12.5 mg/mL	0.48
90	12	12.5 mg/mL	0.96
120	23.75	125 mg/mL	0.19
150	48.75	125 mg/mL	0.39
180	55	125 mg/mL	0.44

*Adapted from Isabwe et al.[474]

TABLE LXIII. Insulin formulations, additives, and concentrations for skin testing[522,532,933]

Insulin formulation; manufacturer	Duration of action	Protamine	Other additives	Stock concentration	SPT concentration	IDT dilutions (0.02 mL)
Insulin aspart (NovoLog); Novo Nordisk	Rapid	None	Metacresol 1.72 mg/mL, glycerin 16 mg/mL, phenol 1.5 mg/mL, zinc oxide 19.6 µg/mL	100 IU/mL	100 IU/mL	1 IU/mL 10 IU/mL
Insulin glulisine (Apidra); Sanofi	Rapid	None	Metacresol 3.15 mg/mL, tromethamine 6 mg/mL, polysorbate-20 0.01 mg/mL	100 IU/mL	100 IU/mL	1 IU/mL 10 IU/mL
Insulin lispro (Humalog U-100); Eli Lily	Rapid	None	Metacresol 3.15 mg/mL, glycerin 16 mg/mL, zinc oxide 19.7 µg/mL (46 µg/mL for U-200)	100 IU/mL (200 IU/mL for U-200)	100 IU/mL	1 IU/mL 10 IU/mL
Regular insulin (Humulin R U-100); Eli Lily	Short	None	Metacresol 2.5 mg/ml, glycerin 16 mg/mL, zinc oxide 17 µg/100 IU	100 IU/mL (500 IU/mL for U-500)	100 IU/mL	1 IU/mL 10 IU/mL
Regular insulin (Novolin R); Novo Nordisk	Regular	None	Metacresol 3 mg/mL, glycerol 16 mg/mL, zinc oxide 7 µg/mL	100 IU/mL	100 IU/mL	1 IU/mL 10 IU/mL
Lily Sterile Diluent (1-ND 800); Eli Lily	NA	None	Metacresol 1.6 mg/mL, glycerin 16 mg/mL	NA	Undiluted	1:100 1:10 (dilutions)
Insulin NPH (Novolin N); Novo Nordisk	Intermediate	Protamine sulfate ~0.35 mg/mL	Metacresol 1.5 mg/mL, glycerol 16 mg/mL, phenol 0.65 mg/mL, zinc ~33.5 µg/mL (vial) and 32.2 µg/mL (FlexPen)	100 IU/mL	100 IU/mL	1 IU/mL 10 IU/mL
Insulin NPH (Humalin N); Eli Lilly	Intermediate	Protamine sulfate 0.35 mg/mL	Metacresol 1.6 mg/mL, glycerin 16 mg/mL, phenol 0.65 mg/mL, zinc oxide 25 µg/mL, glycerin 16 mg/mL	100 IU/mL	100 IU/mL	1 IU/mL 10 IU/mL
Humalog 75/25; Eli Lilly	Intermediate	Protamine sulfate 0.28 mg/mL	Metacresol 1.76 mg/mL, glycerin 16 mg/mL, phenol 0.715 mg/mL, zinc oxide 25 µg/mL	100 IU/mL	100 IU/mL	1 IU/mL 10 IU/mL
Novolog 70/30; Novo Nordisk	Intermediate	Protamine sulfate 0.32 mg/mL	Metacresol 1.72 mg/mL, glycerin 16 mg/mL (Flexpen only), phenol 1.5 mg/mL, zinc 19.6 µg/mL, mannitol 36.4 mg/mL	100 IU/mL	100 IU/mL	1 IU/mL 10 IU/mL
Insulin detemir (Levemir); Novo Nordisk	Intermediate/long	None	Metacresol 2.06 mg/mL, glycerin 16 mg/mL, phenol 1.8 mg/mL, zinc 65.4 µg/mL	100 IU/mL	100 IU/mL	1 IU/mL 10 IU/mL
Insulin glargine (Lantus, Optisulin); Sanofi-Aventis	Long	None	Metacresol 3 µg/mL, glycerin 1.7 mg/mL, zinc 3 µg/mL, polysorbate-20 2 µg/mL*	100 IU/mL	100 IU/mL	1 IU/mL 10 IU/mL
Protamine sulfate; Fresenius Kabi	NA	10 mg/mL	Parabens	10 mg/mL	1 mg/mL[532] 10 mg/mL[522,532]	0.0001 mg/mL[522]

IU, International unit; *NPH*, neutral protamine Hagedorn.
*For 10-mL vial, 3-mL cartridge has no polysorbate-20 and ×3.3 higher concentrations for all other additives.

TABLE LXIV. Short-acting insulin testing

Insulin	SPT concentration (IU/mL)	IDT dilutions (IU/mL)
Novolog (insulin aspart)	100 IU/mL	1 IU/mL 10 IU/mL
Humalog (lispro)	100 IU/mL	1 IU/mL 10 IU/mL
Apidra (glulisine)	100 IU/mL	1 IU/mL 10 IU/mL
Lily Sterile Diluent	Undiluted	1:100 dilution

IU, International unit.

TABLE LXV. Desensitization protocol for regular/NPH insulin by subcutaneous injection*

Step	Time (min)	Dose administered (units)	Type of insulin	Cumulative dose (units)
1	0	0.01	Regular	0.01
2	30	0.02	Regular	0.03
3	60	0.05	Regular	0.08
4	90	0.1	Regular	0.18
5	120	0.2	Regular	0.38
6	150	0.5	Regular	0.88
7	180	1	Regular	1.88
8	210	2	Regular	3.88
9	240	5	Regular	8.88
10	60 min after previous dose	10	NPH	18.88
11	12 h after previous dose	10	NPH	28.88

NPH, Neutral protamine Hagedorn.
*Blood glucose by fingerstick should also be checked every 60 min during steps 1 to 10, and per routine thereafter. After the completion of this protocol, the patient should remain on NPH 10 units twice a day. His endocrinologist can then gradually increase the insulin dose in the outpatient setting, because this dose is likely not adequate.

TABLE LXVI. Progesterone skin testing protocol[541,542]

Diagnostic modality	Progesterone concentration (mg/mL)*
Skin test	50
Intradermal	0.05
	0.5
	5

*Diluent benzyl alcohol or olive oil.

exposure. Use of high-dose progestogens in women undergoing *in vitro* fertilization may predispose them to the development of PH and make it difficult for patients to undergo fertility treatment.[543] Therefore, a careful history of both symptom timing and exposures is critical to making the diagnosis of PH.

Major symptoms. PH is a multisystem disorder. It is characterized by skin lesions, which include urticaria, eczema, erythema multiforme, papulopustular lesions, vesiculobullous and vesiculopustular lesions, as well as angioedema.[545-547] Nondermatologic hypersensitivity symptoms have also been described, including asthma and anaphylaxis.[546,548] Both nondermatologic and dermatologic manifestations have been described in the same patient.[546]

Diagnosis. Diagnosis is primarily based on clinical symptoms correlating with progestogen exposure. Skin testing for PH may be used in the appropriate clinical context to confirm possible cases of PH. The results must be interpreted with caution because the sensitivity and specificity are unknown and false-positive reactions frequently occur.[542] This may be due to the progesterone vehicle because it is not water soluble and must be dissolved in an oil- or ethanol-based diluent. Therefore, the skin testing diluent should be included as a control in addition to appropriate saline (negative) and histamine (positive) controls. Table LXVI lists a published skin testing protocol. An unconvincing history, regardless of skin test result, should prompt the clinician to consider a broader differential diagnosis. Because approximately half of patients with PH have positive skin test results and there are concerns about false-positive testing results, response of symptoms to administration of a gonadotrophin-releasing hormone agonist has been proposed as an alternative diagnostic strategy, at least for those with symptoms from endogenous exposure.[542,549]

Management. Management of PH varies widely on the basis of patient's symptoms and long-term goals. First-line treatment includes symptom management with antihistamines and/or oral or topical steroids as appropriate. In patients who do not experience relief with symptomatic therapies, additional therapies such as oral contraceptive pills, tamoxifen, attenuated androgens, gonadotropin-releasing hormone agonists, and omalizumab can be considered.[550-553] However, these therapies may have long-term adverse side effects limiting patient tolerance. In extreme cases of endogenously triggered PH, oophorectomy remains a curative option.[554]

Progesterone desensitization has been demonstrated as a safe and efficacious option for PH management. Consideration must be given to premedication, trained staff, and clinical settings before initiating desensitization.[543] Indications for desensitization include need for high-dose progesterone therapy for fertility

TABLE LXVII. Progesterone desensitization protocols

A. Intravaginal progesterone desensitization[541]

Time (h)	Dose (mg)*
00:00 (first day)	0.1
00:45	1
01:30	5
02:15	10
03:00	25
00:00 (next day)	50
00:45	100
01:30	100

B. Intramuscular progesterone desensitization[542]

0 min	1
30 min	2
60 min	4
90 min	8
120 min	16
150 min	18.5
Total dose	50
Target daily dose	Intravaginal progesterone 50-90 mg† depending on IVF protocol

C. Slow oral progestin desensitization‡[542]

Day	Dose (based on norethindrone component)	No. of capsules × capsule dose per day	Total daily dose
1	1.25 μg in AM, 2.5 μg in PM	1 × 1.25 μg; 2 × 1.25 μg	3.75 μg
2	2.5 μg in AM, 12.5 μg in PM	2 × 1.25 μg; 1 × 12.5μg	15 μg
3	12.5 μg in AM, 25 μg in PM	1 × 12.5 μg; 2 × 12.5 μg	37.5 μg
4	37.5 μg in AM, 37.5 μg in PM	3 × 12.5 μg; 3 × 12.5 μg	75 μg
5	50 μg in AM, 75 μg in PM	1 × 50 μg; 1 × 50 μg + 2 × 12.5 μg	125 μg
6	250 μg	2 × 125 μg	250 μg
7	500 μg	4 × 125 μg	500 μg
8	500 μg	4 × 125 μg	500 μg
9	1 mg	1 × 1 mg	1 mg

IVF, *In vitro* fertilization.
*Dosing based on target progestogen concentration.
†8% gel once daily.
‡Target dose: norethindrone 1 mg/ethinyl estradiol 0.02 mg.

treatment and persistent hypersensitivity symptoms. For women undergoing *in vitro* fertilization, intravaginal and intramuscular desensitization has been used (Table LXVII, *A* and *B*).[542,543] These cases are often managed in conjunction with a reproductive endocrinologist to optimize desensitization timing. Slow oral desensitization has been proposed for patients with dermatitis refractory to standard therapies (Table LXVII, *C*).[542] Subsequently, patients must continuously cycle on an oral contraceptive to maintain a steady state of progesterone to avoid resensitization.

Glatiramer acetate (Copaxone) (by Elena Crestani, MD)

General. Glatiramer acetate (Copaxone) is a mixture of small polypeptides approved by the FDA as a first-line disease-modifying agent in the treatment of patients with relapsing-remitting multiple sclerosis, given its ability to decrease the frequency of relapse and the progression of disability in affected individuals.[555] It is administered as a 1-mL subcutaneous injection, either daily (20 mg/mL) or 3 times per week (40 mg/mL).

Major symptoms of hypersensitivity. Immediate injection-site reactions are very common, occurring in up to 60% of the patients, and present with erythema, edema, and pruritus.[556] These reactions are thought to be due to direct mast cell activation at the site of injection causing the release of histamine and other mediators. Other local reactions have also been described in the literature, thought to be caused by either direct drug toxicity (skin necrosis, lobular panniculitis) or immunomodulation (erythema nodosum, urticarial vasculitis).[557-563] About 10% of patients experience an immediate postinjection systemic reaction characterized by various combinations of flushing, hives, chest pain, anxiety, subjective sensation of dyspnea, and throat constriction. These reactions can develop at any time during treatment with glatiramer acetate, even after prolonged use, and their severity usually prompts discontinuation of treatment, which otherwise offers a relatively benign side-effect profile. This can be detrimental, especially for those patients who may not be candidates for other treatments. Although some of these reactions may represent true IgE-mediated anaphylaxis, other immediate—and occasionally delayed—cases are associated with negative allergy testing and are likely due to alternative immunologic mechanisms.[561,564-567]

TABLE LXVIII. Glatiramer acetate desensitization protocol*[567]

Solution	Volume (mL)	Concentration (mg/mL)	Timing	Dose (mg)	Cumulative dose (mg)
1	0.5	0.000002	0:00	0.000001	0.000001
2	0.5	0.00002	0:30	0.00001	0.000011
3	0.5	0.0002	1:00	0.0001	0.000111
4	0.5	0.002	1:30	0.001	0.001111
5	0.5	0.02	2:00	0.01	0.011111
6†	0.5	0.2	2:30	0.1	0.1
7	0.5	2	3:00	1	1
8	0.2	10	3:30	2	3
8	0.3	10	4:00	3	6
9	0.2	20	4:30	4	10

*After successful desensitization, start treatment with 10 mg twice daily for 2 doses and then switch to 20 mg daily if no reactions.
†Numbers rounded at step 6.

TABLE LXIX. Rapid desensitization protocol for intravenous administration of imiglucerase (1500 IU)[578]

Solution	Step	Rate (mL/h)	Time (min)	Dose administered with each step (units)	Cumulative dose (units)
1	1	2.0	15	0.0300	0.0300
1	2	5.0	15	0.0750	0.1050
1	3	10.0	15	0.1500	0.2550
1	4	20.0	15	0.3000	0.5550
2	5	5.0	15	0.7500	1.3050
2	6	10.0	15	1.5000	2.8050
2	7	20.0	15	3.000	5.8050
2	8	30.0	15	4.5000	10.3050
3	9	7.0	15	10.4279	20.7329
3	10	15.0	15	22.3454	43.0783
3	11	30.0	15	44.6909	87.7691
3	12	80.01	177.75	1412.2309	1500.0000

IU, International unit.
Description: *Solution 1*, 0.060 U/mL; *Solution 2,* 0.600 U/mL; *Solution 3*, 5.959 U/mL.
Total administration time: 5.71 h.
Premedication: dimetindene, 4 mg administered intravenously 20 min before rapid desensitization.

TABLE LXX. Protocol for vaccine graded dose administration/desensitization*

Step	Volume (mL)	Dilution
1	0.05	1:10
2	0.05	Full strength
3	0.1	Full strength
4	0.15	Full strength
5	0.2	Full strength

*Adapted with permission from Kelso et al.[586]

Diagnosis. Skin prick testing is performed using the full concentration of 20 mg/mL of glatiramer acetate (which is negative in nonexposed controls). If prick testing result is negative, intradermal testing is performed using 0.00002 mg/mL (1:1,000,000 dilution), and if still negative, 0.0002 mg/mL (1:100,000 dilution), which is the highest nonirritating concentration reported in a study.[568] Previous reports indicated a high rate of false-positive reactions in control subjects when higher concentrations were used. Also, each 20-mg vial of glatiramer acetate contains 40 mg of mannitol, which is an irritant that could at least in part be responsible for the high frequency of nonspecific reactions reported.[569,570] Specific IgE to glatiramer acetate have been measured via ELISA in a few patients and levels were found to be elevated in most, though not all, patients with positive skin testing result.[567,569] These determinations were performed on a research basis, because specific IgE testing is not available commercially. Finally, BAT was reported in a series of 3 patients with systemic reactions and positive skin testing result, and the result was positive in 2 of them. Overall, though glatiramer acetate skin testing has not been validated, it appears to be the most useful diagnostic tool to assist in the evaluation and management of patients with a history of reactions to glatiramer acetate to determine whether an IgE-mediated mechanism may be involved; this could help in making a decision about future desensitization if indicated.

Management. Successful desensitization to glatiramer acetate in the context of immediate IgE-mediated hypersensitivity has

TABLE LXXI. Clinical presentation of immediate hypersensitivity according to the modified *Ring and Messmer* Scale[603,608-611]

Grades	Clinical signs
I	Mucocutaneous signs: generalized erythema and/or extensive urticaria with or without angioedema
II	Moderate multivisceral signs: mucocutaneous signs ± hypotension ± tachycardia ± moderate bronchospasm ± gastrointestinal disturbances
III	Life-threatening mono or multivisceral signs: Cardiovascular collapse, tachycardia or bradycardia ± cardiac dysrhythmia ± mucocutaneous signs ± severe bronchospasm ± gastrointestinal disturbances
IV	Circulatory arrest

TABLE LXXII. Classification of LAs mostly used in the perioperative setting

Amides	Esters
Bupivacaine	Chloroprocaine
Levobupivacaine	Procaine
Lidocaine	Tetracaine
Mepivacaine	
Prilocaine	
Ropivacaine	

been described both in adult and in pediatric patients. A report in 2010 described a desensitization protocol that was successfully applied to 6 adult patients with a history of both immediate or delayed systemic reactions and positive skin testing result.[571] Also, a modified, more gradual version of the protocol, which included premedication with steroids and antihistamines, was successfully carried out to desensitize another adult patient.[572] A similar protocol was applied to a 51-year-old woman with generalized urticarial and positive skin testing result to glatiramer acetate.[569] The youngest patient ever documented to undergo successful desensitization was a 14-year-old girl who experienced a severe systemic reaction and was found to have positive skin testing result; she was successfully desensitized to the full dose of 20 mg of glatiramer acetate (10 mg every 12 hours) and was eventually transitioned to daily injections (20 mg daily) with no further adverse reactions[568] (Table LXVIII). The same protocol has been successfully used to desensitize another pediatric patient, and doctors were able to switch the patient to daily dosing within 24 hours of desensitization. H_1 and H_2 blockers, antileukotriene, or leukotriene receptor antagonists may be used for pretreatment and/or treatment of breakthrough reactions.

Imiglucerase (Cerezyme) (by Joseph Zhou, MD, PhD)

General. Imiglucerase (Cerezyme) is a highly purified human enzyme used for long-term enzyme replacement therapy for type 1 Gaucher disease. Up to 15% of patients may experience adverse reactions.[573] Reported adverse events include gastrointestinal irritation (nausea, vomiting, abdominal pain, diarrhea), nonspecific constitutional symptoms (fatigue, fever, headache, chills, rash, and backache), and tachycardia. Approximately 15% of patients have developed IgG antibodies, and although more than 90% of these patients tolerated the infusion for at least 24 to 36 months, almost half of these antibody-positive patients later experienced symptoms suggestive of hypersensitivity.[574,575] In general, hypersensitivity reactions to imiglucerase intravenous infusion have been reported in approximately 13.8% of patients. IgE-mediated hypersensitivity reactions caused by imiglucerase are not common, and anaphylaxis to imiglucerase infusion is rare (reported in <1% of patients).[576,577]

Given the detrimental consequence of anaphylaxis, patients with symptoms suggesting hypersensitivity reaction to imiglucerase need to be evaluated carefully and managed accordingly. Skin testing and graded challenge can be used to evaluate imiglucerase hypersensitivity. Desensitization for continued administration of imiglucerase can be considered in patients who have an established diagnosis of imiglucerase hypersensitivity without appropriate alternative therapy.

Evaluation. The positive and negative predictive value of imiglucerase skin test is unknown due to limited data; therefore, skin testing is not recommended as a routine procedure. However, if the clinical symptoms associated with imiglucerase infusions suggest possible IgE-mediated hypersensitivity, skin testing and/or graded challenge with imiglucerase solution can be considered. Skin testing is recommended only for those patients who experience moderate or severe recurrent imiglucerase infusion—associated reactions and the reactions are suggestive of IgE-mediated hypersensitivity such as persistent symptoms of bronchospasm, hypotension, and/or urticaria.

Imiglucerase is reconstituted at the concentration of 200 units in 5 mL of sterile water to make a 40 units/mL solution. This concentration can be used for skin prick testing. For intradermal testing, 10-fold serial dilutions can be made with 0.9% sterile saline, and the highest nonirritating concentration for intradermal testing is 4 units/mL.[573] Provider discretion can be used regarding the least concentrated dilution at which to start testing.

For patients who experience mild adverse reactions to imiglucerase infusion that are not consistent with a hypersensitivity reaction, imiglucerase may be delivered with 2- or 3-step graded challenge protocols depending on the severity of the adverse reaction. If a 3-step protocol is used, 1% of the total therapeutic dose can be infused over 1 hour as the first step. If there are no adverse reactions at the end of the infusion, the infusion rate can be increased so that 10% of the total dose is delivered over 1 hour. The rest of the therapeutic dose (90%) can be given at the regular rate if the patient successfully tolerates the first 2 steps. If no adverse events are noted at the end of the third-step infusion, the patient is not likely to have imiglucerase allergy, and the challenge is not needed in the future unless the patient develops new reactions that may suggest hypersensitivity.

Management. Desensitization is recommended for patients who have hypersensitivity reactions to imiglucerase and have no alternative treatment. An example protocol could include 5 bags (from 1 unit/mL to 0.0001 unit/mL) with 10 steps each to deliver roughly 140 units of imiglucerase in 5 hours. Then another 4-step infusion protocol can be used to achieve the regular infusion rate of 100 mL/h at the final step.[573] The total desensitization time varies depending on the dose but typically takes 6 to 9 hours.

TABLE LXXIII. Concentrations of anesthetic agents normally nonreactive during skin tests[611]

Drugs		PTs		IDTs	
International nonproprietary name	Concentration (mg/mL)	Dilution	Maximal concentration (mg/mL)	Dilution	Maximal concentration (μg/mL)
Atracurium	10	1/10	1	1/1000	10
cis-Atracurium	2	Undiluted	2	1/100	20
Mivacurium	2	1/10	0.2	1/1000	2
Pancuronium	2	Undiluted	2	1/10	200
Rocuronium	10	Undiluted	10	1/200	50
Suxamethonium	50	1/5	10	1/500	100
Vecuronium	4	Undiluted	4	1/10	400
Etomidate	2	Undiluted	2	1/10	200
Midazolam	5	Undiluted	5	1/10	500
Propofol	10	Undiluted	10	1/10	1000
Ketamine	100	1/10	10	1/100	1000
Alfentanil	0.5	Undiluted	0.5	1/10	50
Fentanyl	0.05	Undiluted	0.05	1/10	5
Morphine	10	1/10	1	1/1000	10
Remifentanil	0.05	Undiluted	0.05	1/10	5
Sufentanil	0.005	Undiluted	0.005	1/10	0.5
Bupivacaine	2.5	Undiluted	2.5	1/10	250
Lidocaine	10	Undiluted	10	1/10	1000
Mepivacaine	10	Undiluted	10	1/10	1000
Ropivacaine	2	Undiluted	2	1/10	200

TABLE LXXIV. Maximum nonirritating concentrations for skin testing of opiods[79]

Drug	Skin prick (mg/mL)	Intradermal (mg/mL)
Morphine	1	0.01
Fentanyl	0.05	0.005
Alfentanil	0.5	0.05
Sufentanil	0.005	0.0005
Remifentanil	0.05	0.005

TABLE LXXV. Desensitization protocol for sublingual buprenorphine*[663]

Step (30 min apart)	Dose (sublingual)
1	0.002 μg
2	0.02 μg
3	0.2 μg
4	0.002 mg
5	0.02 mg
6	0.2 mg
7	0.6 mg
8	1.2 mg

*For target dose of 2 mg sublingual buprenorphine twice daily with cetirizine 10 mg premedication followed by daily administration.

A few more case reports regarding successful imiglucerase desensitization have been reported by Peroni et al[574] (a 7-step rush protocol, total infusion time of 4 hours, final infusion rate of 400 units/h), Erdogdu et al, [578] and Tsilochristou et al.[579] The 12-step protocol for administration of 1500 units of imiglucerase over 5.7 hours is presented in Table LXIX.[578]

Vaccines (by Matthew Giannetti, MD)

General. The reported incidence of *any* adverse effect after vaccine administration is 11.4 per 100,000, of which fever and injection-site reactions are most common.[580] The incidence of IgE-mediated hypersensitivity is much lower. One retrospective US study analyzed data from 2009 to 2011 and reported 33 of 25,173,965 cases of anaphylaxis with no deaths (1.31 cases/million doses).[581] Another study reported an incidence of immediate hypersensitivity to be 1 of 450,000 vaccines administered. Thirty-one percent of reactions occurred after the first administration of the vaccine, thus suggesting preexisting sensitization.[582]

Clinical manifestations. Clinical symptoms can be divided into immediate and delayed reactions. Immediate reactions occur minutes to hours after vaccination and may include urticaria/angioedema, flushing, pruritus, wheezing, dyspnea, and hypotension.[583] Delayed reactions occur more than 60 minutes after vaccination and include rash, fever, and joint pain.[584] Symptoms such as fever and injection-site edema are not considered manifestations of hypersensitivity and should not preclude future doses of the vaccine.[585]

Diagnosis. IgE-mediated reactions are more likely to be directed at vaccine components than the active ingredient.[584] Causative components include gelatin, egg protein, latex, and yeast. Therefore, skin testing should encompass the vaccine and

all potential culprit components contained in the vaccine. When skin testing to the vaccine itself, testing should use an identical vaccine (same dose and manufacturer) as that which caused the reaction.

Skin prick testing should begin with full-strength vaccine. If the PT result is negative (with appropriate controls), proceed to intradermal testing using 0.02 mL of a 1:100 dilution.[586] Skin testing to gelatin, egg, latex, and yeast should be conducted in the usual manner. If skin testing is not possible (standardized latex and gelatin are not routinely available in the United States), substitution with *in vitro* specific IgE-antibody assays is appropriate, though sensitivity is typically lower with specific IgE testing.[587] If testing result is positive, the patient must be considered allergic. Negative skin testing result virtually excludes the possibility of an IgE antibody to the vaccine or vaccine component.[586]

Management. Patients who present with mild symptoms that are not compatible with IgE-mediated hypersensitivity may be administered the vaccine in the usual manner. Exceptions include absolute contraindications such as Guillain-Barré, SJS, encephalopathy, and other severe delayed reactions.

All patients who report symptoms consistent with IgE-mediated hypersensitivity should undergo skin testing. Since negative skin testing virtually excludes the presence of an IgE-mediated reaction, these patients may be given the vaccine in the usual manner, followed by a 30-minute observation period.[586] Alternatively, one-tenth of the vaccine may be administered, followed by a 30-minute observation period, then the remaining dose. Patients with positive skin testing result are more likely allergic to the vaccine; however, patients with positive skin testing result have also received the vaccine uneventfully. If additional doses are required, these should be administered using a graded dose protocol (Table LXX). In all cases, appropriate medication should be available for immediate treatment as necessary.

Patients with a preexisting allergy to a vaccine component (*without* previous exposure to the vaccine itself) may warrant further evaluation. Patients with gelatin allergy should undergo skin testing to gelatin before receiving the varicella zoster, measles-mumps-rubella, or rabies vaccines.[588] Gelatin skin testing is typically not available in the United States; testing for both bovine and porcine gelatin specific IgE is an appropriate alternative. However, Kelso et al[586] describe a gelatin preparation made by dissolving 1 teaspoon (5 g) of any sugared gelatin powder (eg, Jell-O) in 5 mL of normal saline to create an SPT solution, recognizing that this is not a standardized, validated, FDA-approved method. Patients allergic to egg require evaluation before receiving the yellow fever vaccine (all other vaccines are safe in patients with egg allergy).[589,590] Patients akkergic to yeast should be evaluated before receiving the hepatitis B and human papillomavirus vaccines. Evaluation should include serum-specific IgE to *Saccharomyces cerevisiae* (baker's yeast) and/or skin prick testing to *S cerevisiae*. Finally, a history of immediate hypersensitivity to latex, neomycin, streptomycin, or polymyxin B warrants evaluation before the administration of a vaccine containing these compounds. Positive skin testing result should prompt desensitization to the necessary vaccine.

Table LXX assumes a vaccine with a standard volume of 0.5 mL. Each dose should be followed by a 15-minute observation before proceeding to the next step. After completion, the patient should be observed for 30 minutes.

LOCAL AND GENERAL ANESTHETICS AND OPIATES

Perioperative immediate hypersensitivity (by Pascale Dewachter, MD, PhD, and David L. Hepner, MD, MPH)

Epidemiology. In the early 1980s, the overall incidence of perioperative immediate hypersensitivity was estimated to be 1 in 5,000 to 13,000 anesthetics administered in Australia, 1 in 4,600 in France, 1 in 1,250 to 5,000 in New Zealand, and 1 in 3,500 in the United Kingdom.[591-594] By the end of the 1990s, the overall incidence of perioperative IgE-mediated anaphylaxis was 1 in 1,000 to 20,000 anesthetics administered in Australia and 1 in 13,000 in France.[595,596] Recently, over the last decade, the combined allergic and nonallergic anaphylaxis rate with an anesthetic was estimated to be 1 in 11,000 in Western Australia and 1 in 10,000 in the United Kingdom.[597,598] More precisely, an IgE-mediated mechanism has been involved in half and up to two-thirds of the cases of perioperative immediate hypersensitivity in the United States, Spain, Norway, and France.[599-602] Perioperative IgE-mediated allergy mainly occurs after anesthetic induction and is primarily linked to neuromuscular-blocking agents (NMBAs) and antibiotics such as β-lactam drugs; it may also arise during the maintenance phase of anesthesia and agents unrelated to anesthetics are then usually involved.[603] A female predominance has been regularly reported for both IgE-mediated and non−IgE-mediated hypersensitivity reactions, irrespective of the causal agent, whereas immediate IgE-mediated drug allergy is uncommon in children.[599-602] The incidence of perioperative latex allergy continues to decrease.

The morbidity rate of perioperative IgE-mediated anaphylaxis remains unknown. The latest *National Audit Project* (NAP6) reported a mortality rate of 3.8% among 266 reports of anaphylaxis from all UK National Health Service hospitals over 1 year (November 2015 to November 2016).[598] In contrast, a previous Western Australian retrospective study (January 2000 to December 2009) suggested that perioperative anaphylaxis mortality rate is within the range of 0% to 1.4% and that the higher rates, that is, 3% and up to 10%, reported during the last 2 decades may be an overestimate.[597,604-607]

In summary, the incidence of perioperative anaphylaxis likely remains underestimated because not all cases are investigated, reported to the *Drug Safety Monitoring Authorities*, or included in a national register. Conversely, the related mortality seems to be lower than previously reported.

Clinical presentation. Perioperative immediate hypersensitivity mainly occurs within minutes after anesthetic induction and is primarily linked to agents administered intravenously.[603] The initial diagnosis of perioperative immediate hypersensitivity is based on the ongoing features and their severity, as well as the timing between the introduction of the suspected drug and the onset of clinical symptoms. The clinical presentation of perioperative nonallergic hypersensitivity is usually mild or moderate and less severe than that of IgE-mediated allergic hypersensitivity, this latter condition being mostly life-threatening.[603,608] The care management of perioperative immediate hypersensitivity is guided by the clinical expression of the reaction.[600,609-612]

TABLE LXXVI. Desensitization protocols for AERD and non-AERD NSAID hypersensitivity reactions

Aspirin desensitization for patients with AERD*		
Oral protocols		
	Time	**Aspirin dose (mg)**
Two-day protocol		
Dose escalation	180 min	
Day 1	8:00 am	20-40†
	11:00 am	40-60
	2:00 pm	60-100
	5:00 pm	Discharge
Day 2	8:00 am	150
	11:00 am	325
	2:00 pm	Discharge
One-day protocol		
Dose escalation	90 min	
	8:00 am	40.5†
	9:30 am	81
	11:00 am	162
	12:30 pm	325
	2:00 pm	Discharge
Intranasal ketorolac and oral aspirin protocol		
Day 1	8:00 am	1.26 mg ketorolac† (1 spray in 1 nostril)
	8:30 am	2.52 mg ketorolac (1 spray in each nostril)
	9:00 am	5.04 mg ketorolac (2 sprays in each nostril)
	9:30 am	7.56 mg ketorolac (3 sprays in each nostril)
	10:30 am	60
	12:00 pm	60
	3:00 pm	Discharge
Day 2	8:00 am	150
	11:00 am	325
	2:00 pm	Discharge
Aspirin desensitization for patients without AERD‡		
Option 1: Dose escalation: Every 15-30 min until target daily dose has been tolerated[682]		
Day 1	0	1
	15	2
	30	5
	45	10
	60	20
	75	40
	90	81§
Option 2: Dose repeated every 90 min until no further reaction symptoms[682]		
Day 1		
	0	40.5
	90	40.5§
	180	Repeat 40.5 only if patient reacts§
Recommendations for treatment of NSAID-induced reactions		
Respiratory		Bronchodilators and zileuton if severe
Nasal/ocular		H_1 antagonists, topical decongestants
Cutaneous		H_1 antagonists and zileuton if severe
Gastrointestinal		H_2 antagonists and zileuton if severe
Hypotension		Intramuscular epinephrine
Laryngeal		Racemic epinephrine

*Pretreatment with leukotriene receptor antagonists is strongly recommended for all AERD protocols.
†Lung function and vital signs are monitored before each dose and at the onset of a reaction. Reaction symptoms are treated for patient safety and comfort. Once symptoms subside, typically within 3 h, the threshold dose is repeated and the dose-escalation interval resumes.
‡No medication pretreatment recommended for rapid oral protocols.
§On subsequent days, start aspirin 81 mg daily.

How to stratify immediate hypersensitivity. Although the Ring and Messmer 4-step grading scale does not take into account the pathophysiologic mechanisms involved (allergic vs nonallergic), it is appropriate for grading the clinical severity of drug-induced immediate hypersensitivity into 4 categories (grades I-IV) and guiding its clinical care. This 4-step grading scale, widely used in Europe, has been adapted as follows for the perioperative setting (Table LXXI).[603,608-611] Grade I reactions involve mucocutaneous signs only, whereas grade II reactions correspond to mucocutaneous features that may be associated with mild cardiovascular (hypotension, tachycardia) and/or respiratory signs. The cardinal sign of grade III reactions is cardiovascular collapse, which may be associated with mucocutaneous signs and bronchospasm. Grade IV reactions present with circulatory arrest. Thus, grade I and II reactions are not life-threatening conditions and usually of nonallergic origin but sometimes may be IgE-mediated. However, grade III and IV reactions are typically being referred to as *anaphylaxis,* that is, a life-threatening immediate hypersensitivity more likely to be IgE-mediated. All these grades thus require subsequent allergologic investigation.

Major symptoms. Cardiovascular homeostasis disturbances are the hallmark of drug-induced perioperative immediate hypersensitivity. These cardiovascular features are usually associated with mucocutaneous signs and may be associated with respiratory symptoms. Non−IgE-mediated immediate hypersensitivity may include mucocutaneous signs alone or hypotension associated with tachycardia and mucocutaneous signs. The most common pattern of perioperative drug-induced IgE-mediated allergy is consistent with cardiovascular collapse usually associated with tachycardia, or in some cases with bradycardia and cutaneous features (generalized erythema and/or extensive urticaria). These cutaneous features are sometimes associated with mucous signs (eyelid and/or lip angioedema). Particularly during the maintenance phase of anesthesia, cutaneous signs may be initially missed because of surgical drapes. In grade III reactions, the cardiovascular collapse may rapidly evolve into cardiac arrhythmia and/or circulatory arrest if not recognized and/or treated appropriately. Cardiovascular collapse as the sole feature or circulatory arrest may also be the inaugural event of perioperative drug-induced allergic anaphylaxis.[608-612] In this setting, circulatory arrest usually presents as pulseless electrical activity.[598,603,613,614]

Mucocutaneous signs (eg, generalized erythema) are usually present since the early stage of anaphylaxis but may be absent before the restoration of hemodynamic parameters. Bronchospasm may also be present, especially in patients with poorly controlled underlying airway hyperreactivity (eg, asthma and chronic obstructive pulmonary disease [COPD]). In contrast, isolated bronchospasm is never of allergic origin.[615] Gastrointestinal signs are usually not reported during the perioperative setting.[603,608]

Tako-Tsubo syndrome following perioperative anaphylaxis. Tako-Tsubo syndrome is characterized by an acute but reversible left ventricular systolic dysfunction and shares common features with acute coronary syndrome.[616] This condition has been previously described under different names including *broken heart syndrome* or *stress cardiomyopathy* or *apical ballooning syndrome*. Recently, an international expert consensus provided diagnostic criteria for the diagnosis of Tako-Tsubo syndrome to improve its identification and stratification.[617,618] The main diagnostic criteria include the following: (1) transient left ventricular dysfunction; (2) electrocardiographic abnormalities (rare cases may exist without any electrocardiographic changes); (3) levels of cardiac biomarkers (troponin and creatine kinase) moderately elevated in most cases; significant elevation in level of brain natriuretic peptide is common; (4) neurologic disorders (eg, subarachnoid hemorrhage and stroke) and pheochromocytoma may serve as triggers; and (5) emotional and/or physical triggers may precede the syndrome.

Four major variants of Tako-Tsubo syndrome have been described, based on the anatomic distribution of regional wall motion abnormalities. The left ventricular apical ballooning, also known as the typical form of Tako-Tsubo syndrome, is the most common phenotype. Atypical phenotypes include wall motion patterns in the basal, midventricular, and focal anatomic areas. Tako-Tsubo syndrome following perioperative anaphylaxis has been published. In this setting, inappropriate high doses of exogenous epinephrine appear to be the common trigger.[619,620] The basal phenotype has been reported to be associated with epinephrine-induced Tako-Tsubo syndrome, which is characterized by a rapid onset of symptoms after epinephrine administration.[617,620] However, the contributive role of endogenous catecholamines in response to anaphylaxis cannot be ruled out.[621]

Agents involved. Perioperative IgE-mediated anaphylaxis usually occurs within minutes of anesthetic induction.[608] In this clinical setting, NMBAs and antibiotics (mainly β-lactam agents) are the main drugs involved.[599,601,602] Anaphylaxis may also arise during the maintenance phase of anesthesia and is usually due to agents unrelated to the anesthetic. These agents given during a surgery include dyes (methylene blue, patent blue V and its derivative isosulfan blue), colloid (modified fluid gelatin), antiseptics (chlorhexidine, povidone iodine), iodinated contrast agents, aprotinin (some fibrin glue products contain aprotinin), and other biological sealants.[603,608] Ethylene oxide−induced anaphylaxis has also been suggested as a cause of perioperative anaphylaxis. However, it appears that most of the reactions attributed to ethylene oxide were due to latex.[622] Systemic cooling has also been reported as a trigger for perioperative anaphylaxis.[623] Finally, anaphylaxis may also occur toward the end of the anesthetic induction or during the recovery period after the injection of sugammadex or neostigmine used for NMBA reversal.[624,625]

Neuromuscular-blocking agents. NMBAs are quaternary ammonium compounds with positively charged radicals [$N^{+}(CH_3)_3$] mimicking the quaternary nitrogen radical of acetylcholine. This similarity in structure attracts NMBAs to nicotinic receptors. NMBAs can be classified according to their mechanism of action, as depolarizing and nondepolarizing agents. Succinylcholine, a depolarizing agent, is an agonist at acetylcholine receptors. Nondepolarizing agents are competitive antagonists at the acetylcholine receptor and grouped according to their chemical structure into steroidal (pancuronium, rocuronium, vecuronium) and benzylisoquinolin (atracurium, cis-atracurium, and mivacurium) compounds.

All NMBAs may elicit IgE-mediated allergic immediate hypersensitivity, which is usually a life-threatening condition, that

TABLE LXXVII. Oral challenge protocols for acetaminophen*

	Acetaminophen dose (mg)	
Step	Rojas-Perez-Ezquerra et al[697]	Yilmaz et al[693]
1	250	10
2	500	50
3	1000-Final	250
4		500-Final

*Doses separated by 1-h intervals.

TABLE LXXVIII. Details of diagnostic testing to thienopyridines[706]

Immediate hypersensitivity testing*	Delayed hypersensitivity testing†
Clopidogrel 75 mg/mL	Clopidogrel (20% in petroleum alba and 30% in water)
Step 1: Epicutaneous: 1/100 dilution	
Step 2: Intradermal: 1/1000 dilution	
Step 3: Intradermal : 1/100 dilution	
Ticlopidine 6.25 mg/mL	Ticlopidine (75% in water)
Step 1: Epicutaneous: 1/100 dilution	
Step 2: Intradermal: 1/1000 dilution	
Step 3: Intradermal: 1/100 dilution	
Prasugrel 5 mg/mL	Prasugrel (5% in water)
Step 1: Epicutaneous: 1/10 dilution	
Step 2: Intradermal: 1/100 dilution	
Step 3: Intradermal: 1/10 dilution	

*Epicutanous PTs and IDTs were performed with same concentration in this series, but a further 1:10 dilution is suggested for intradermal testing.
†Patch tests read at 48 and 72 h.

is, grade III reaction, and in some rare cases, consistent with an inaugural grade IV reaction.[603,626] The substituted (tertiary as well as quaternary) ammonium ions have been suggested to be the allergenic determinants of NMBAs since the 1980s.[627,628] Although cross-reactivity between NMBAs is common, it is unusual that an individual is allergic to all NMBAs.[629] Cross-reactivity refers to the drug allergenicity and to the allergenic profile of the patient.

A higher prevalence of serum IgE antibodies to tertiary and/or quaternary ammonium ions among blood donors and atopic patients was reported in Norway but not in Sweden. The only difference in environmental chemical exposure was the use of cough syrups containing pholcodine available only in Norway.[630] Other work demonstrated a higher prevalence of serum IgE antibodies to tertiary and/or quaternary ammonium ions and/or to pholcodine, morphine, and suxamethonium after pholcodine exposure in atopic patients and in a few patients with a history of NMBA-induced anaphylaxis.[630-632] The use of drugs containing pholcodine was therefore questioned, because of the potential risk for NMBA hypersensitivity.[631,632] However, no relationship has been clinically established between these increased IgE levels and the occurrence of NMBA allergy during a subsequent anesthetic. The *European Medicines Agency* therefore stated that the existing evidence does not support the use of pholcodine-containing medicines as a risk for developing NMBA allergy.[633]

Currently, the only known risk factor for NMBA-allergic hypersensitivity is a previous noninvestigated immediate hypersensitivity reaction that occurred during a previous anesthetic induction conducted with an NMBA.[609-611,626] Nevertheless, uneventful previous exposure to an NMBA does not exclude the risk for IgE-mediated allergy during a subsequent anesthetic induction.[608,609] In addition, NMBA allergy may occur without previous NMBA exposure.[609,611,626,628]

Finally, benzylisoquinoline NMBAs, such as atracurium and mivacurium (both are not available in the United States), may directly stimulate histamine release (ie, nonallergic immediate hypersensitivity), whereas cis-atracurium does not.

Sugammadex. Sugammadex is a modified γ-cyclodextrin with a lipophilic core and hydrophilic periphery. It is used to reverse neuromuscular blockade by encapsulating steroidal NMBAs (rocuronium, vecuronium) and displacing them from their receptors. Cyclodextrins are made up of dextrose units (α-, β-, and γ-cyclodextrins). Sugammadex-induced immediate allergic hypersensitivity has been reported.[625] The γ-cyclodextrin unit that contains 8 thiopropionate side chains may be responsible for hypersensitivity reactions.

Neostigmine. Neostigmine is structurally similar to acetylcholine but contains a carbamate group instead of the acetyl group. Neostigmine is an inhibitor of the enzyme acetylcholinesterase, which hydrolyzes the neurotransmitter *acetylcholine* at synapses. Accumulation of acetylcholine at the neuromuscular junction competitively antagonizes nondepolarizing NMBAs. A few IgE-mediated cases of allergy to neostigmine have been reported.[624,634]

Hypnotic agents. *Propofol*: Propofol is an alkylphenol derivative (2,6-di-isopropylphenol) marketed as an oil-water emulsion using 10% soybean oil, 2.25% glycerol, and 1.2% egg lecithin as the emulsifying agent. This intravenous induction agent is widely used. Propofol may directly stimulate histamine release, especially in young and/or stressed patients experiencing

cutaneous signs (eg, localized or extensive erythema).[635] Conversely, IgE-mediated allergic hypersensitivity to propofol remains extremely rare relative to its widespread use.[609-611] The few documented propofol-induced IgE-mediated reactions have been shown to be elicited by the isopropyl or phenol groups rather than the lipid vehicle. A retrospective investigation of 171 anesthetic charts from 99 patients with elevated specific IgE to egg, soy, or peanut showed no documented IgE-mediated allergy to propofol.[636] According to this study and previous reports, there is no reason to avoid propofol in patients with allergy to egg, soy, and peanut.[626,636]

Other intravenous induction drugs: IgE-mediated allergic hypersensitivity to midazolam (hydrosoluble benzodiazepine) is extremely rare relative to its widespread use.[79,610,611] Ketamine is a hydrosoluble aryl-cyclo-alkylamine. There is no documented report of IgE-mediated allergic hypersensitivity to this drug.

Inhaled anesthetics. Halogenated general anesthetic agents are volatile liquids administered by inhalation of the vapor. The chemical structures of these agents include fluorinated methyl-ethyl-ethers (desflurane, isoflurane) and a poly-fluorinated-isopropyl-methyl-ether (sevoflurane). There is no report of IgE-mediated allergic hypersensitivity to these volatile anesthetics.

Opioids. Morphine is a tertiary amine that, when insufficiently diluted, causes nonspecific direct histamine release leading to false-positive skin test results.[610,611] Alfentanil, fentanyl, remifentanil, and sufentanil belong to the phenylpiperidine derivatives and have no local effect on mast cells. No IgE-mediated allergy has been reported with alfentanil, remifentanil, and sufentanil. A few cases of immediate allergy to fentanyl have been reported, but the diagnosis has not been proven because of methodologic issues.[637,638]

Local anesthetics. Local anesthetics (LAs) belong to the ester or amide groups (Table LXXII). Ester LAs (procaine, chloroprocaine, and tetracaine) have a lipophilic or aromatic group, an intermediate ester linkage, and a hydrophilic residue with a tertiary amine. The metabolism of ester LAs is via plasma cholinesterases. Para-aminobenzoic acid is the common metabolite of ester LAs inducing immediate and delayed hypersensitivity reactions. Cross-reactivity is the rule among esters due to para-aminobenzoic acid.

Amide LAs, such as lidocaine, mepivacaine, prilocaine, bupivacaine, levobupivacaine, and ropivacaine, differ from esters in that they have an intermediate amide linkage. The metabolism of amide LAs is primarily in the liver. IgE-mediated allergy to amide LAs is extremely rare relative to their widespread use.[609-611] Most reported reactions are vasovagal episodes or toxic reactions from inadvertent intravascular injection of an LA or epinephrine. Delayed hypersensitivity to amide LAs has also been reported. Cross-reactivity in the amide group has been established for immediate and delayed hypersensitivity reactions.[639-641] There is no cross-reactivity between amide and ester LAs.

Chlorhexidine. Perioperative IgE-mediated allergy to chlorhexidine is being increasingly recognized in Denmark and the United Kingdom but not in France.[598,642,643] In a retrospective (July 2004 to July 2012) single-center study, specific IgE and skin tests (including PTs and IDT) to chlorhexidine were completed in 228 patients investigated for suspected perioperative allergic reactions.[642,643] About 10% of examined cases met criteria for chlorhexidine allergy defined as a relevant clinical reaction combined with 2 or more positive test results. The highest combined estimated sensitivity and specificity was found for specific IgE and SPT to chlorhexidine.

Latex. The incidence of perioperative latex allergy is drastically decreasing.[600,602] This is because most hospitals now use powder-free latex gloves with negligible residual protein concentrations and/or nonlatex gloves.[635] In addition, the use of natural rubber latex in medical products and/or equipment has been reduced. Latex-induced immediate allergy is now infrequently reported in the perioperative setting.

Diagnosis. The etiologic diagnosis of perioperative immediate hypersensitivity is linked to a triad including clinical evidence along with biological and allergologic results.[609-612] The interpretation of the biological and allergologic assessment should always be correlated to the careful and complete review of the clinical history including the management care. The joint analysis of these elements helps to determine the pathomechanism involved (allergic vs nonallergic), identify the culprit agent, and provide subsequent and appropriate advice for further anesthetics.

In vivo biochemical tests. *Plasma histamine*: Plasma histamine is a preformed inflammatory mediator stored in mast cells and basophils. An elevated concentration of plasma histamine indicates *in vivo* release and is observed during both allergic and nonallergic immediate hypersensitivity. The peak of plasma histamine is immediate (normal <10 nmol/L), and its plasma elimination half-life is short (~15-20 minutes). Diamine-oxidase enzyme inactivates histamine in humans and shows the highest expression in the intestine, kidney, and placenta. Because the enzymatic activity of diamine-oxidase increases several hundred-fold during gestation compared with nonpregnant individuals and plasma histamine rapidly decreases in a concentration-dependent manner to levels below 1 ng/mL, plasma histamine should not be measured after the first trimester of pregnancy.[609-611,644]

Plasma histamine should ideally be measured within 15 minutes after the onset of clinical features in cases of grade I reaction, within 30 minutes after a grade II reaction, and within 2 hours in grade III and IV reactions. [609-611]

Tryptase: Tryptases are neutral serine proteases stored predominantly in mast cells. *In vivo*, 2 major forms can be measured. *Pro-α tryptase* reflects mast cell burden and is elevated in mastocytosis. Mature β-*tryptase* is preferentially stored in mast cells granules and is released during episodes of mast cell activation, such as IgE-mediated allergy. The total tryptase level (normal <11 or 13 μg/L) measures both forms. *Tryptase can be measured* in *serum* or *plasma.* Total tryptase concentrations reach a peak at 1 hour after the onset of the reaction and decline under first-order kinetics (elimination half-life of ~90 minutes). [609-612] Although an increase in tryptase can be measured 30 to 60 minutes after the onset of symptoms in cases of mild reactions (eg, nonallergic immediate hypersensitivity due to histamine release), it may not be elevated. Sampling is recommended within 30 minutes and 2 hours in cases of grade III and IV reactions.[611,612] An increase in tryptase is highly suggestive of mast cell activation, but its absence does not preclude the diagnosis of IgE-mediated anaphylaxis. Baseline tryptase level should be obtained more than 24 hours after the clinical event or when the

patient is referred for investigation and compared with acute tryptase levels.[645,646]

Histamine and tryptase concentrations correlate with the severity of the clinical reaction.[13,611] Combined histamine and tryptase measurements are recommended for the diagnosis of perioperative immediate hypersensitivity in the United States and France.[13,611,635] The British and Scandinavian guidelines only recommend tryptase measurement.[609,610] The collection of 24-hour histamine metabolites (urinary methyl-histamine) is also recommended in the United States, because it is elevated for a longer duration of time than plasma histamine.[13,635] Its measurement has been discontinued in Europe.[609-611]

In vitro biochemical tests. *Specific serum IgE measurement*: *In vitro* tests detect the presence of IgE antibodies by binding the allergen onto a solid phase and using radioactive system detection (radioallergosorbent test) or by binding the allergen onto a sponge matrix using fluorescent detection (fluoroimmunoassay or CAP system).[13,609-611] Radioallergosorbent test is now rarely used.

In vitro tests have been developed for the detection of specific IgEs directed to the tertiary or quaternary ammonium groups of NMBAs using a quaternary ammonium (choline chloride). They work by coupling an analogue of choline onto a polysaccharide support on sepharose or *p*-aminophenylphosphoryl-choline on agarose, the latter being marketed only in France.[647,648] Subsequently, a morphine-based solid-phase IgE was proposed, because the tertiary methyl-amino group of morphine cross-reacts *in vitro* with NMBAs.[649]

In Europe, the suxamethonium-specific assay is currently available among the different commercialized NMBAs. Its sensitivity is relatively low, around 30% to 60%.[629] Specific serum IgE measurement is also available for other drugs including β-lactams (eg, ampicillin and amoxicillin and penicillins G and V), morphine, chlorhexidine, and protamine in Europe and only to penicillin G and V in the United States. However, these *in vitro* specific IgE assays to drugs are less sensitive and specific when compared with skin testing.[13,609-611] Thus, identification of serum IgE to certain drugs provides possible evidence of IgE sensitization but does not prove by itself that the drug induced the immediate hypersensitivity reaction.[609]

In addition, IgE-antibody assay is commercially available for latex. Although skin testing has a higher sensitivity (95%-99%) compared with IgE testing (35%-76%), a skin test reagent to latex is not commercially available in the United States.[650] IgE-antibody testing may be performed at the time of the reaction or later.[609-611]

Basophil activation test. BAT is a sophisticated technique using flow cytometry, which allows quantifying the *ex vivo* capacity of sensitized blood basophil activation. The upregulation of certain markers (CD63 and CD203c) present on the granule membrane is expressed on the basophil membrane on activation with the suspected allergen. BAT might add to the etiologic diagnosis of immediate drug hypersensitivity (eg, NMBA) and help to identify both cross-reactive and safe alternative compounds.[609-611] However, this technique is not commercially available. The latest recommendations provided by the ENDA and the Drug Allergy Interest Group of the EAACI stated that BAT is recommended for diagnosing NMBA immediate hypersensitivity and, when available, BAT should be performed before skin testing, especially in life-threatening reactions.[651] However, a recent study showed that combined CD63 and CD203c markers did not increase BAT sensitivity compared with CD203c alone in the investigation of NMBA immediate hypersensitivity. BAT allowed identification of the culprit drug in 80% of patients with allergy to NMBA and yielded concordant cross-reactivity results in only 60% of the cases compared with skin tests results. The authors thus conclude that BAT combining CD63 and CD203c markers does not replace skin testing in the assessment of NMBA allergy.[645] However, BAT is not commercially available and the role of BAT needs to be better defined in the diagnostic approach of NMBA-induced immediate hypersensitivity, because skin testing is more sensitive than *in vitro* tests.[609-611]

Skin testing. Skin testing remains the *criterion standard* for the detection of IgE-mediated allergy versus nonallergic immediate hypersensitivity. All drugs to which the patient was exposed within minutes before the clinical reaction must be skin tested.[609-612] Investigation of anesthetics is performed by PTs followed by IDTs using commercialized solutions undiluted or diluted without exceeding the maximum recommended concentrations (ie, corresponding to the maximum nonirritant drug concentration).[79,609-611,629] PTs may produce false-negative results, whereas IDTs are more sensitive but less specific than PTs.[609,610] However, IDTs are more likely to trigger a systemic allergic reaction and, thus, should be performed only if PT results are negative.[609,610] Diagnostic criteria for a positive skin test result (including PT and IDT) and maximum recommended concentrations have been defined in France.[611] They have been recommended and/or adapted by others, and endorsed by EAACI/ENDA (Table LXXIII).[79,609,610,629]

Skin testing should be performed according to the pathomechanism of the immediate hypersensitivity reaction and thus interpreted by reading it within 15 to 20 minutes of the skin test. If the PT results are negative, IDT is performed by injecting 0.03 to 0.05 mL of the corresponding drug (eg, beginning at 1:10,000 or 1:1,000 dilution). If the IDT result is negative, a 10-fold increased concentration is used with incremental 15- to 20-minute intervals between each IDT until the test result is positive or the highest nonirritant concentration is achieved.

It is usually recommended that skin testing be done at least 4 to 6 weeks after the clinical reaction to avoid false-negative test results.[652] Dialysis and heavy tobacco smoking may lead to a decreased response due to cutaneous vasoconstriction, whereas cutaneous reactivity may be increased in cases of dermographism. Finally, skin testing can be performed at any point during the pregnancy, especially for LAs and NMBAs.[611]

In conclusion, a suggestive clinical history with a mild reaction without an increase in tryptase and a negative skin test result is indicative of a nonallergic reaction, such as histamine release. The use of preoperative H_1-receptor antagonists reduces the clinical effects of histamine release. Conversely, immediate hypersensitivity reactions requiring emergency treatment, and associated with an increased tryptase and positive skin test results to the suspected drug/agent, constitute evidence of an IgE-mediated mechanism.[609-612] In this latter condition, the identified drug/agent should be avoided in the future, whereas negative skin-tested drugs can be used for further procedures.[608,611]

- *NMBAs:* The sensitivity of skin tests to NMBAs in patients having experienced NMBA anaphylaxis is greater than 95%, and their reproducibility is excellent.[611] Testing should be done by PTs, followed by IDTs. When skin testing result with an NMBA is positive, investigation for cross-reactivity with other available NMBAs should be performed to identify a safe alternative (ie, negative skin-tested NMBAs) for further procedures.[608,611,645,653]
- *Sugammadex:* Sugammadex may be skin tested undiluted by PTs followed by IDTs if PT is negative (up to 1/100 dilution, which appeared nonirritant).[625]
- *Neostigmine:* Neostigmine may be skin tested undiluted by PTs followed by IDTs if PT is negative (up to 1/100 dilution, which appeared nonirritant).[628]
- *Hypnotic agents:* These drugs may be skin tested undiluted by PTs, followed by IDTs (up to 1/10 dilution) if PT results are negative.[79,611]
- *Opioids:* Phenylpiperidines may be skin tested undiluted by PTs followed by IDTs if PT results are negative (1/10 dilution should not be exceeded). However, 1/10 and 1/1000 morphine dilutions are recommended for PT and IDT, respectively.[79,611]
- *LAs:* LAs (without epinephrine) may be skin tested undiluted by PTs followed by IDTs if PT is negative (1/10 dilution should not be exceeded).[79,611] A protocol for subcutaneous incremental challenge (graded challenge) involves injections of increasing volumes of LA to which the patient has been proven to be skin-tested negative. A single-blind saline step is done 15 to 20 minutes after the skin PT to rule out nonallergic causes. Following this (typically 15-20 minutes), 0.1 mL, 0.5 mL, and 1 mL of undiluted subcutaneous injections of LA are used as challenge steps. It is ideal to wait 15 to 20 minutes between steps.[654]
- *Chlorhexidine:* Chlorhexidine (without alcohol) may be skin tested up to 5 mg/mL by PTs followed by IDTs (up to 0.002 mg/mL) if PT is negative.[79]
- *Latex:* In contrast to the United States, in Europe, latex allergy investigation is performed by PTs using commercial extracts. The sensitivity of skin tests with latex is excellent.

Opioids and buprenorphine (by Parul Kothari, MD)

General

Opioids are generally used to treat both acute and chronic pain. The Drug Enforcement Agency classifies opioids in 5 different scheduling classes on the basis of their potential for abuse and addiction, which are the main concerns with their long-term use. Structurally, opioids can be placed into the following 4 chemical classes[655]:

- Phenanthrenes, whose members include morphine, codeine, hydromorphone, oxycodone, hydrocodone, oxymorphone, and buprenorphine.
- Benzomorphans, which include only pentazocine as a member.
- Phenylpiperidines, which include fentanyl, alfentanil, sufentanil, and meperidine.
- Diphenylheptanes, which include propoxyphene and methadone.

In addition, based on their interaction with the μ, κ, and δ receptors, opioids can be classified as agonists (eg, morphine), partial agonists (eg, buprenorphine), or antagonists (eg, naloxone), with the latter used to treat opioid overdose.

Major symptoms of hypersensitivity. True type I immediate hypersensitivity reactions to opioids are rare and are limited to case reports in the literature.[656-658] Most adverse reactions to opioids are side effects, often due to nonspecific, direct release of mast cell mediators through interactions with the mast cell opioid receptor. However, it is often difficult to distinguish between these 2 possibilities because their clinical manifestations can overlap. Both can cause pruritus, flushing, urticaria, nausea, vomiting, bronchospasm, and hypotension. DHRs to opioids have also been reported.[659,660]

Diagnosis. Although some case reports have demonstrated the presence of specific IgE via skin or serum testing, currently there is no validated test for diagnosing an immediate hypersensitivity reaction.[656-658] Skin testing with narcotics can lead to nonspecific release of mast cell mediators, thereby eliciting a wheal-and-flare response even in the absence of specific IgE.[661] As such, distinguishing between immune- and nonimmune-mediated reactions is based on a careful history as well as physical examination findings at the time of the reaction. Nonirritating concentrations for skin testing that have been reported are presented in Table LXXIV.[79]

Although ACD has been reported for several different opioids, it appears to be most commonly associated with transdermal buprenorphine.[659,660] In these small case series, the diagnosis was confirmed with patch testing, and the ability to tolerate other opioids (oral and/or transdermal) was demonstrated. In 1 case, oral buprenorphine was given without any adverse reaction.

Management. Prevention of future reactions will depend on the underlying mechanism. Nonspecific adverse reactions, a class effect, can be inhibited by pretreating with antihistamines and/or steroids, using lower doses, or using opioids with less histamine-releasing properties, such as fentanyl.[662] However, for immune-mediated hypersensitivity reactions, strict avoidance of the culprit and metabolites is recommended. As such, because codeine is metabolized to morphine, patients who are able to tolerate codeine but react to morphine are unlikely to have a true allergy but those with evidence of an IgE-mediated allergic reaction to morphine should also avoid codeine.

For patients with evidence of an immediate or delayed hypersensitivity to an opioid, currently data to determine the risk of cross-reactivity within and across different structural classes are limited. Case reports and series have shown that most patients with an allergic reaction are able to tolerate at least 1 other opioid but too few patients have been studied to make accurate predictions. Thus, if a patient requires treatment with a narcotic, it is recommended to use one that has been tolerated previously. If that information is not known, one should determine which alternative agent(s) could be safely administered by performing an oral challenge in a monitored setting. There are currently no standardized desensitization protocols for narcotic analgesics, but a desensitization protocol to sublingual buprenorphine has been reported for a non−IgE-mediated reaction (Table LXXV).[663] The serial dilutions for desensitization were made by grounding and suspending buprenorphine sublingual tablets (2 mg). Given the lack of data on the stability of buprenorphine in solution, dilutions were prepared close to the time of administration to minimize any possible loss of potency.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Aspirin (by Katherine N. Cahill, MD, and Ari J. Fried, MD)

General. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are unified by their ability to inhibit cyclooxygenase (COX)-1. Any inhibitor of COX-1 can cause acute or delayed hypersensitivity reactions. Aspirin-induced reactions are generally the result of altered eicosanoid pathways following COX-1 inhibition. The ease of access to NSAIDs and their clinical utility make them one of the leading causes of hypersensitivity reactions. The reported prevalence of hypersensitivity reaction to aspirin and other COX-1 inhibitors in children is 0.3% and in adults is 1.9%; the prevalence among patients with asthma is an estimated 5% in children and 7.2% in adults.[664-667] True NSAID hypersensitivity needs to be distinguished from an adverse reaction or intolerance to an NSAID such as tinnitus or gastrointestinal bleeding.

Major symptoms of hypersensitivity. Cross-reacting COX-1 inhibitor reactions include (1) aspirin-exacerbated respiratory disease (AERD), (2) NSAID-exacerbated cutaneous disease, and (3) NSAID-induced urticaria and/or angioedema.[17] Acute NSAID hypersensitivity reactions that do not cross-react are known as selective NSAID-induced urticaria, angioedema, and/or anaphylaxis. Selective NSAID-induced delayed reactions such as mild maculopapular exanthems, SJS, TEN, fixed drug eruptions, DRESS, pneumonitis, aseptic meningitis, and nephritis are much less common than acute reactions (Table LXXVI).[668] Both acute and delayed reactions have been reported in children and adults.[669]

AERD is unique among the NSAID-exacerbated reactions with the associated comorbidities of asthma and nasal polyposis. NSAID-exacerbated reactions in AERD include nasal congestion, rhinorrhea, postnasal drip, ocular injection, ocular and oropharyngeal pruritus, and bronchospasm within 15 to 180 minutes of NSAID exposure. Less frequently, angioedema, urticaria, macular eruptions, abdominal pain, nausea, vomiting, diarrhea, and hypotension have been reported. AERD is generally considered an adult-onset disease, but AERD has been reported to develop as early as at age 8 years.[670]

Diagnosis. The diagnostic workup for identification of NSAID hypersensitivity is the same for children and adults. Distinguishing selective COX inhibitor hypersensitivity from cross-reactive hypersensitivity is crucial to determine the best strategy for further management. The evaluation has to start with a careful analysis of the history including symptom pattern and time course of the reaction.

Oral aspirin challenge is the criterion standard for the diagnosis of AERD.[671] NSAID-exacerbated cutaneous disease (NECD) patients have chronic urticaria and a history of an acute flare of urticaria and/or angioedema from NSAID, while patients with NSAID–induced urticaria and/or angioedema (NIUA) have had acute urticaria and/or angioedema from NSAID, and do not have an associated chronic respiratory or cutaneous condition. Patients with either NECD or NIUA exhibit cross-reaction to structurally unrelated COX-1 inhibitors—which should be avoided. Challenge procedures are commonly performed to aspirin in these patients when aspirin 81 mg daily is required for cardioprotection. Desensitization is not recommended in the setting of NECD but can be accomplished in patients with NIUA. For patients with a history suggesting selective NSAID-induced urticaria, angioedema, and/or anaphylaxis, a challenge to another COX-1 inhibitor can be performed to rule out a cross-reacting NSAID hypersensitivity.[17,672] The role of skin testing or basophil activation testing to NSAIDs has not been validated and is not recommended. Serum-specific IgE has been reported in a case series of pyrazolone-induced anaphylaxis, a class of NSAIDs no longer available in the United States.[673] The detection of serum-specific IgEs for other NSAIDs has not been reported. In the setting of severe delayed reactions, reexposure to the culprit agent is not recommended and exposure to another member of the NSAID class can be considered if medically necessary. With rare exception, selective COX-2 inhibitors are tolerated by patients with a history of COX-1 hypersensitivity reactions, but reactions to selective COX-2 inhibitors in patients with a history of COX-1 inhibitor hypersensitivity have been reported; as a precaution it may be appropriate to administer the initial dose under observation based on clinical circumstances.[674]

Management. Although challenge protocols confirm the diagnosis and subtype of NSAID hypersensitivity, desensitization protocols provide a means to allow the patient to safely tolerate daily aspirin (Table LXXVI).[675] Aspirin challenge or desensitization followed by daily aspirin therapy is indicated for adult and pediatric patients with AERD who require revision polypectomies or frequent or daily corticosteroid therapy. Any patient with a history of an acute NSAID hypersensitivity reaction with a medical indication (cardiovascular or rheumatologic disease) for aspirin or other COX-1 inhibitor should be offered desensitization.[676] Before initiating a challenge or desensitization protocol, it is recommended that FEV_1 be greater than 60% predicted and at least 1.5 L. Use of a leukotriene receptor antagonist in advance of the desensitization in patients with AERD decreases the severity of bronchospasm.[677] In a small subset of patients with AERD, the use of leukotriene receptor antagonists will completely mask the symptoms of a reaction. However, it is generally accepted that the added safety benefit from their use outweighs this risk. Inhaled or oral corticosteroids and long-acting bronchodilators should be continued and asthma should be optimized at the time of desensitization, with oral steroids added if necessary. Oral antihistamines and decongestants are discontinued 48 hours before and short-acting β-agonists the morning of desensitization to avoid masking a clinical reaction. Challenge/desensitization protocols for AERD can take place in the outpatient setting, including for pediatric cases, with the exception of patients with recent myocardial infarction, continuous β-blocker therapy, or uncontrolled asthma.[678]

A standard oral aspirin desensitization protocol for AERD begins with a dose of 40 mg of aspirin, with dose escalation every 90 to 180 minutes, as outlined in Table LXXVI. At the onset of reaction symptoms, the patient is monitored and symptomatic treatment with β-agonists, antihistamines, nasal decongestants, and 5-lipooxygenase inhibitors can be used to ensure patient safety and comfort. Shorter oral protocols have been reported in the literature.[679] Alternatively, a modified protocol using intranasal ketolorac is available that reduces extrapulmonary reactions during desensitization.[680] Once a patient has tolerated 325 mg of aspirin without evidence of symptoms, they can increase their dose of aspirin to the recommended treatment dose of 650 mg twice daily at home. If aspirin is discontinued for more than 48 hours, the desensitized state can be lost and repeat desensitization is recommended. In the event of a planned surgical procedure during which aspirin should be avoided, the daily aspirin dose

can be decreased to 81 mg leading up to the procedure, held the day before and the morning of the procedure, and immediately resumed after the procedure is completed.

For other non-AERD reactions to NSAIDs, challenge protocols are published.[675] In clinical practice, there is less consensus about the dose and timing intervals for challenge/desensitization due to the wide range of clinical history, reaction severity, and subtype of NSAID hypersensitivity encountered. Aspirin is the preferred agent in a desensitization protocol for non-AERD NSAID hypersensitivity because there are no verified reports of anaphylaxis from aspirin.[681] For those with non-AERD NSAID hypersensitivity and a clinical indication for daily aspirin use such as after cardiac stent placement, aspirin challenge or desensitization using 1 of 2 rapid protocols has demonstrated success.[682] Both protocols reach the established antiplatelet threshold of 81 mg within 2 to 3 hours (Table LXXVI).

Acetaminophen (by Samantha Minnicozzi, MD)

Acetaminophen is one of the most commonly used drugs in the world. It is a medication that is generally well tolerated, and it is frequently used as an alternative agent for patients with aspirin hypersensitivity.[683] Hypersensitivity reactions are exceedingly rare, with limited data and reports of suspected IgE-mediated reactions. There are numerous case reports and some case series describing anaphylaxis or anaphylactoid reactions to acetaminophen.[683-696]

Acetaminophen is classified as an NSAID, but it is a weak cyclooxygenase inhibitor and does not provide any anti-inflammatory effects.[683] However, a number of patients who are aspirin intolerant can also be intolerant of acetaminophen, and some acetaminophen-specific reactions can also be either dependent on or independent of dose.[684,689,691,692]

Major symptoms of hypersensitivity. In a review of acetaminophen hypersensitivity reactions reported over a 4-year period to a private allergy clinic in France, 84 patients were identified.[683] Of these 84 patients, 13 were considered identified to have an allergy based on history and oral challenge testing. Their symptoms consisted of maculopapular eruptions, urticaria, bronchospasm, rhinitis, and laryngeal edema.[683] Other case reports highlight patients who experience similar symptoms but also have hypotension, vomiting, and/or diarrhea.[686,690,694,697]

In addition to immediate hypersensitivity reactions, case reports in the literature have described acetaminophen's association with SJS reactions.[698]

Diagnosis. The validity of skin testing to acetaminophen is unknown. However, in case reports citing skin prick and intradermal testing at various concentrations, all control subjects have been negative.[685,687,688,692,696,697] Of the skin testing protocols proposed, many are not feasible because the sterile forms required for intradermal testing do not exist in many countries. Currently, the only intravenous formulation of acetaminophen is a single concentration of 10 mg/mL. This only allows for intradermal testing to occur with dilutions of this formulation. The protocol described by Rojas-Perez-Ezquerra et al[697] uses the intravenous formulation of acetaminophen with a concentration of 10 mg/mL for skin prick testing, and a dilution of 1 mg/mL as well as the undiluted 10 mg/mL for intradermal testing. However, patients and control subjects in that study tested negative on skin prick and intradermal testing.

Other reviews published on acetaminophen allergy use solely SPTs up to concentrations of 200 mg/mL despite evidence elsewhere demonstrating that concentrations more than 10 mg/mL can be known irritants leading to false positives for drugs.[688,692,696]

Management. Of the studies identifying patients with a history concerning for acetaminophen hypersensitivity, the current recommendations for definitive evidence of a reaction are oral-based challenge tests.[696] This is because of the relatively infrequent occurrence of hypersensitivity reactions associated with acetaminophen use.[683,688,689,695] Table LXXVII highlights the common methods of graded challenges performed for both suspicion of anaphylaxis and NSAID-related reactions.[693,696] A recent meta-analysis including 259 patients who underwent oral challenges to acetaminophen for diagnostic confirmation or exclusion estimates the prevalence of true acetaminophen hypersensitivity to be 10.1% in adults and 10.2% in pediatric patients.[699]

ANTICOAGULANTS AND COAGULATION FACTORS

Clopidogrel and antiplatelet agents (by Kimberly Blumenthal, MD)

General. Clopidogrel (Plavix) is a selective, irreversible inhibitor of ADP-induced platelet aggregation for oral use. It belongs to the class of second-generation thienopyridine antiplatelet agents. Within ADP2Y12 platelet receptor inhibitors, there are thienopyridines (clopidogrel, prasugrel, and ticlopidine) or cyclopentyl-triazolo-pyrimidines (ticagrelor and cangrelor). Clopidogrel is the standard of care for patients who have undergone coronary stenting, especially in drug-eluting stents. Additional indications include acute management of myocardial infarctions, peripheral artery disease, or cerebral vascular accident. The incidence of hypersensitivity reactions to clopidogrel have been reported to range from 1% to 6% of exposures, with most estimates ranging from 1% to 3%.[700-702]

Major symptoms. The most common hypersensitivity reaction to clopidogrel is rash, commonly macular, morbilliform, or diffuse and erythematous, beginning about 5 days into treatment.[703,704] In addition to these likely T-cell—mediated drug eruptions, IgE-mediated reactions comprise about 5% to 7% of clopidogrel hypersensitivity reactions.[705,706] In 1 case series, patients with urticaria represented 17% of reactions to clopidogrel.[707] Worldwide postmarketing pharmaceutical experience reports that anaphylactic reactions occur in fewer than 1% of cases.[701] Other reactions including systemic hypersensitivity syndromes have been described, including a serum sickness—like reaction, fixed drug eruption, and SJS.[708] Current literature review does not describe DRESS syndrome, TEN, or acute interstitial nephritis attributed to clopidogrel use.

Diagnosis. There is no validated skin testing or patch testing to clopidogrel. However, diagnostic testing could follow the procedures of the largest case series (42 patients) evaluated with both immediate hypersensitivity testing and patch testing after a history suggestive of hypersensitivity to clopidogrel (Table LXXVIII).[706] Of the 42 patients tested, most had a history consistent with a delayed rash. Although none were positive by epicutaneous prick, 3 patients—all with previous symptoms suggestive of an IgE-mediated reaction—were positive on

intradermal testing. Most patients, 34 of 42 or 81%, had positive patch testing result to clopidogrel.[706] Caveats include that there were no documented controls and there are no data to inform a nonirritating skin testing concentration for immediate hypersensitivity skin testing. In addition, the utility of testing for cutaneous eruptions that are not IgE-mediated is unknown, but can be helpful for some cutaneous eruptions, including maculopapular eruptions, AGEP, and fixed drug eruptions.[13,51,709-711]

Management

Alternative agents. Alternative agents could include another thienopyridine (ticlopidine or prasugrel), ticagrelor, warfarin, or cilostazol.

Ticlopidine is as effective as clopidogrel. It is not first-line therapy because of an unfavorable side-effect profile, including serious adverse reactions of neutropenia and thrombotic thrombocytopenic purpura (in 2%). There is concern about cross-reactivity between clopidogrel and ticlopidine because the structure differs only by an addition of a caboxymethyl group and they have shared metabolites *in vitro* (Figure 7). Cross-reactivity determined by patch-test result was found in 24% of patients.[706] Given available data to date, if ticlopidine were to be used in a patient with a history of allergy to clopidogrel, an oral challenge would be advised (Table LXXIX).

Prasugrel is the most potent of the thienopryridines, but it is contraindicated in patients with previous cerebrovascular accident, age more than 75 years, or weight less than 60 kg. There is concern regarding cross-reactivity to clopidogrel, because they are structurally similar (Figure 7). No data currently exist on cross-reactivity between clopidogrel and prasugrel, because the clinical trials for prasugrel excluded patients with a history of allergy to ticlopidine or clopidogrel. One study demonstrated a 17% cross-reactivity with prasugrel using patch testing, and there are reports of patients with a history of allergy to clopidogrel who subsequently tolerated prasugrel.[706,712-714] Given available allergy data, if prasugrel were to be used in a patient with a history of allergy to clopidogrel, or vice versa, an oral challenge would be recommended (Table LXXIX).

Ticagrelor, which is a reversible P2Y12 inhibitor and a strong antiplatelet, is completely structurally dissimilar from clopidogrel. Although a previous report hypothesized cross-reactivity, review of the case and symptoms reported more likely reflected a reaction to the clopidogrel and stronger evidence supports that ticagrelor can be safely administered to patients with clopidogrel hypersensitivity.[715-717]

Oral challenge. An oral graded challenge to clopidogrel would be appropriate if the reaction (1) was unlikely to have been caused by clopidogrel, (2) was not IgE-mediated/serious/life-threatening and the benefits of clopidogrel use outweighed the risk of reaction, and (3) led to initiation of a potentially cross-reactive drug (eg, ticlopidine).

Desensitization. Desensitization protocols for clopidogrel hypersensitivity are safe and successful, and have been used both for IgE-mediated reactions and for delayed cutaneous reactions. Contraindications to desensitization include severe T-cell—mediated reactions such as DRESS, TEN, or SJS. In a study of 24 patients who underwent a desensitization procedure, 100% of the patients had successful desensitization and all patients were taking clopidogrel at the 6-month follow-up. Most patients (83%) did not have reactions during the desensitization procedure.[707] Published desensitization procedures range from 2 to 8 hours (Table LXXX).[718] The 2-hour or 7-hour desensitization procedures are recommended on the basis of severity of the allergy history, considering both the type and severity of the reaction, as well as considering comorbidities and acuity of the patient's illness. Recently, outpatient multiday protocols have been used for patients with clopidogrel hypersensitivity (largely rash, but 1 patient had angioedema) with success.[719] One disadvantage of using a desensitization protocol for clopidogrel hypersensitivity, particularly after stent placement, is that it requires initial cessation of clopidogrel to allow for a washout period and symptom resolution. However, patients may be treated with an alternative agent (eg, ticlopidine) during this period.

Drug continuation with treatment with steroids and antihistamines. Because cardiology data show a significant risk (25%-30%) of thrombosis with interruption of antiplatelet therapy, some groups have used a "treating though" strategy for cutaneous clopidogrel hypersensitivity reactions (Table LXXXI).[720] Sixty-two patients with cutaneous reactions (both urticarial and nonurticarial rashes) to clopidogrel were treated with a 30-mg twice-daily tapering prednisone course and benadryl 25 to 50 mg Q6-8PRN without drug stoppage. This approach was successful in 98% of patients, with the rashes resolving in about 5 days and all patients had uninterrupted dual platelet therapy. Among their 62 patients, this approach failed in 1 patient who developed angioedema and required hospitalization.[706] Among 25 patients with delayed rashes who were treated with steroids (methylprednisolone) and antihistamines (fexofenadine 180 mg every day with 25-50 mg diphenhydramine QHS) for a mean of 10 $\pm$ 8 days without interruption of clopidogrel, 22 of 25 (88%) patients had no adverse effects/events in long-term follow-up, and all completed clopidogrel therapy according to the America Heart Association guidelines.[705] The mean duration of steroid treatment was 10 days. Two patients had recurrent symptoms, treated with more corticosteroids (18 days starting with prednisone 60 mg), an antileukotriene (montelukast 10 mg), and antihistamines. In sum, 3 patients failed this therapy, with 1 patient each having angioedema, a desquamating rash, and intolerable pruritus. Another group used prednisone 30 mg twice a day with cetirizine 10 mg daily with success.[721] Given these encouraging data, this strategy is reasonable for benign, maculopapular, or erythematous eruptions that are likely to be T-cell—mediated and without organ involvement. However, this strategy is not recommended in IgE-mediated reactions, especially those involving organ systems beyond the skin, where desensitization is indicated, or rashes suggestive of a severe T-cell—mediated reaction. Caution is also warranted when using this approach for cutaneous reactions suggestive of IgE (eg, urticaria) given that these studies demonstrating this approach to urticarial rashes are not robust enough to determine the safety of this approach.

Heparin and protamine (by Cosby Stone Jr, MD, MPH, and Allison Norton, MD)

General. Heparin is a widely used anticoagulating agent for the active treatment and prophylaxis of thrombosis in at-risk patients. Side effects of heparin are overall quite rare considering the frequency of its use in hospitalized patients for the prevention

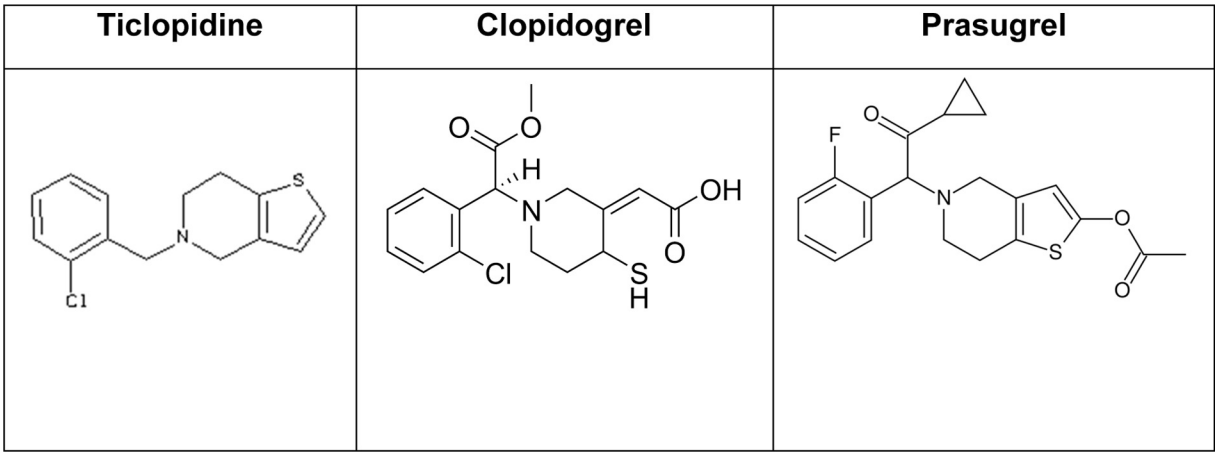

FIGURE 7. Biochemical structures of the thienopyridines.

of deep venous thrombosis. Most reports of hypersensitivity to heparin are DHRs, which can affect up to 7.5% of patients treated, and heparin-induced thrombocytopenia (HIT).[722-724] There are, however, rare reports of immediate hypersensitivity reactions.[725,726] In the past, when heparin products were contaminated with overly sulfated chondroitin sulfates, non−IgE-mediated anaphylaxis was reported via the kinin-kalikrein pathway through the production of bradykinin, as well as C3a and C5a anaphylatoxins.[727] In addition, immediate hypersensitivity to protamine, the main reversal agent for heparin-mediated anticoagulation, has occurred, and can easily be mistaken for an allergy to heparin or insulin.[728,729]

Heparins are sulfated carbohydrates of the glycosaminoglycan family first purified from pig intestines with the property of being naturally occurring activators of antithrombin III, and they achieve their anticoagulation effects by antithrombin III−mediated inactivation of thrombin.[730] Unfractionated heparin (UFH) can include heparins of various molecular weights and lengths, typically averaging 14 to 18 kDa.[722,730] Low-molecular-weight heparins (LMWHs) have been modified by fractionation or depolymerizaton to provide a purified product, in which at least 60% of chains are less than 8 kDa in length, to reduce the biological unpredictability of UFH. Heparinoids are synthetic molecules designed to mimic the binding site of heparin to antithrombin III (Table LXXXII).[722]

Because of their strong negative charge, UFH and LMWHs can be inactivated by the highly cationic peptide protamine, a compound originally derived from salmon spermatozoa. Protamine has itself been shown to cause IgE-mediated hypersensitivity reactions, especially in patients previously exposed to protamine-containing insulins.[13,531,728,731] Fish allergy and vasectomy have previously been alleged as risk factors for protamine reaction, but there is no substantiated evidence to support this claim.[732,733]

Cross-reactivity. Wide ranges of cross-reactivity have been reported to occur in LMWHs in DHR, but fondaparinux and danaparoid are generally well tolerated.[722] Hypersensitivity to UFH is reported to be frequently cross-reactive with LMWHs and heparinoids.[723,726]

Hypersensitivity to heparin is not cross-reactive with structurally distinct anticoagulants such as hirudins or factor Xa inhibitors, and these are often used as alternative agents.[725,734]

Major symptoms of hypersensitivity. Heparins have been demonstrated most commonly to cause DHR, of which the most typical feature is an itching, eczematous plaque, or maculopapular eruption that first appears around sites of injection after 7 to 10 days of continuous initial treatment, and can appear more rapidly on subsequent exposures.[723,726,730,735,736]

Immediate-type hypersensitivity to heparins can present with palmoplantar pruritus, urticaria, conjunctivitis, bronchospasm, and anaphylaxis, and are only rarely reported.[722,726,730,737] Hypotension, angioedema, and swelling of the larynx have developed in patients after receiving heparin products contaminated with oversulfated chondroitin sulfates.[727]

Mild thrombocytopenia is noted in the setting of UFH use in about 30% to 50% of critically ill patients, but severe HIT via IgG specific for large complexes of heparin bound to platelet factor 4 occurs in around 1%.[722,738] HIT usually occurs after 5 days of treatment with either UFH or LMWHs, and, in severe cases, can present with profound thrombocytopenia, thrombosis, or cutaneous necrosis.[13,730,739,740] Immediate reactions can occur on the first dose for previously sensitized patients with HIT, with symptoms including fever, flushing, dyspnea, mental status change, and hypertension.[722]

Immediate hypersensitivity to protamine has been reported with urticaria, hypotension, and anaphylaxis, via IgE- and non−IgE-mediated mechanisms.[13,530,531,728,731,741] Dose-dependent hypotension after rapid infusion of protamine is most likely triggered by nonspecific histamine release.[13] Protamine is a rare cause of intraoperative anaphylaxis and is most often reported during cardiac surgeries when quick reversal of heparin anticoagulation is required.[531]

Cases of delayed hypersensitivity to protamine with erythematous plaques at injection sites can occur to protamine-containing insulin, with 1 report including eosinophilia and renal dysfunction.[742,743]

Diagnosis. Nonirritating concentrations for the evaluation of immediate hypersensitivity to heparins and heparinoids have been reported and shown to be useful in clinical decision

TABLE LXXIX. Ticlopodine test dose protocol (graded oral challenge)

Step 1	1/4 of a pill/dose, observe for 60 min
Step 2	1 pill/full dose, observe for 60 min

TABLE LXXX. Desensitization protocols for clopidogrel[718]

Time (h)	Dose	Concentration	mL
Seven-hour protocol			
0:00	0.005	0.5 mg/mL	0.01
0:30	0.01		0.02
1:00	0.02		0.04
1:30	0.04		0.08
2:00	0.08		0.16
2:30	0.16		0.32
3:00	0.3		0.6
3:30	0.6		1.2
4:00	1.2	5 mg/mL	0.24
4:30	2.5		0.5
5:00	5		1
5:30	10		2
6:00	20		4
6:30	40		8
7:00	75	75-mg tablet	1 tablet
Two-hour protocol			
0:00	0.02	0.5 mg/mL	0.04
0:15	0.05		0.1
0:30	0.15		0.3
0:45	0.5		1
1:00	1.5	5 mg/mL	0.3
1:15	5		1
1:30	15		3
1:45	45		9
2:00	75	75 mg	1 tablet

making.[79,726] Skin testing is generally performed via PT with commercially available undiluted product. IDTs with 1:10 and 1:100 dilution may be useful, though lower concentrations are associated with lower sensitivity.[79] The European concentration for heparin is 25,000 units/mL for prick and 2,500 units/mL for IDT, but the highest US concentration is 10,000 units/mL, so PT with 10,000 units/mL and IDT with 1,000 units/mL is recommended. In clinical experience, because cross-reactivity between UFH, LMWHs, and heparinoids can occur, it is recommended that a panel of all these products be used during testing.[79]

Diagnosis of delayed hypersensitivity to heparins has been reported to be more sensitive when using delayed intradermal testing at 1:10 dilution compared with patch testing. These are typically read 2 to 7 days after placement.[79,723,744]

Testing for IgG antibodies to platelet factor 4 is the mainstay of early diagnosis for HIT when it is suspected clinically, with a sensitivity greater than 90% and quick turnaround times.[738] Serotonin release assays remain the criterion standard for HIT diagnosis in terms of specificity, but they are limited by availability, specialized equipment, and longer time to obtain results.[738]

Immediate hypersensitivity skin testing and serum-specific IgE testing to protamine have been reported in the literature, but have not been well studied and recommended testing dilutions vary widely.[530,728,745] Ebo et al[629] suggest using a maximum undiluted protamine concentration of 50 mg/mL for skin prick testing and 50 μg/mL maximum concentration for intradermal testing. However, a case series using 53 controls suggested that intradermal testing at 30 μg/mL may cause nonspecific histamine release. They suggest skin prick testing at concentrations of 300 to 330 μg/mL and 0.03 to 30 μg/mL for intradermal testing.[532]

Management. Management of heparin sensitivity should focus on choosing an alternative non–cross-reactive agent or desensitization if there is no alternative. Patients with hypersensitivity to UFH are often cross-sensitized to LMWHs, and additionally may be sensitized to heparinoids.[722] Given that the negative predictive value of heparin and protamine skin testing remains unknown, a high suspicion of clinical reactivity with negative testing still warrants desensitization or if feasible, selection of an alternative agent. Generally, patients with both immediate and delayed hypersensitivity can tolerate the nonstructurally related hirudins, factor Xa inhibitors, but rare patients with sensitization to structurally dissimilar anticoagulants have been reported.[722]

TABLE LXXXI. Protocol for treating through cutaneous clopidogrel hypersensitivities[720]

Initial therapy	Continue clopidogrel 75 mg/d
	Methylprednisolone taper (6-d Medrol Dosepak)
	Antihistamines until symptom resolution (fexofenadine 180 mg/d and diphenhydramine 25-50 mg at bedtime)
Secondary therapy for hypersensitivity reoccurrence	Continue clopidogrel 75 mg/d
	Longer course of corticosteroids (up to 18 d, eg, prednisone 60 mg, taper by 10 mg every 3 d)
	Montelukast 10 mg/d
	Antihistamines as needed

TABLE LXXXII. Anticoagulants by structural and functional category

Heparins	Direct thrombin inhibitors	Factor Xa inhibitors
UFH	Hirudins	Apixaban
LMWHs	Bivalirudin	Rivaroxaban
Ardeparin	Desirudin	
Certoparin	Lepirudin	
Dalteparin	Argatroban	
Enoxaparin	Dabigatran etexilate	
Nadroparin		
Reviparin		
Tinzaparin		
Heparinoids		
Danaparoid		
Synthetic heparins		
Fondaparinux		

TABLE LXXXIII. Heparin desensitization protocol*

Step	Solution (U/mL)	Rate (U/h IV)	Time (h)	Volume infused per step (mL)	Dose infused per step (units)	Cumulative dose (units)
1	1	0.5	0-12	6	6	6
2	1	1.5	12-24	18	18	24
3	10	4.5	24-36	5.4	54	78
4	10	13.6	36-48	16.32	163.2	241.2
5	10	40.8	48-60	48.96	489.6	730.8
6	100	122.5	60-72	14.7	1,470	2,200.8
7	100	367.4	72-84	44.09	4,408.8	6,609.6
8	100	1008.0	84-96	120.96	12,096	18,705.6

The patient was preoperative for cardiac bypass and maintained at a dose of 1000 units/h until surgery. Additional desensitization protocols are reviewed in the same reference. Available solution concentrations may vary depending on institution.
*Modified from Dave and Park.[747]

Several case reports have described successful heparin desensitization for immediate hypersensitivity reactions, typically over 4 to 5 days.[746-750] Dave and Park[747] describe a protocol in which heparin doses are continuously infused intravenously over 12-hour periods in half-log 10 increments to a goal infusion of 1000 unit/h of heparin (Table LXXXIII). The patient successfully tolerated a 50,000 unit bolus of heparin after completing this desensitization and a subsequent smaller dose of heparin.

Management of HIT similarly involves immediate cessation of the offending agent, use of alternative anticoagulants, and future avoidance of both UFH and LMWHs.[739]

Because of the nature of its use as a reversal agent, there is little role for desensitization for intraoperative protamine. Management for these reactions typically focuses on modification of operative protocols where it is to be used, because there are no clinically available alternatives to protamine. In the future, there may be alternatives approved by the FDA; there are already several products in advanced clinical phases.[751]

Desensitization to protamine-containing insulin may be necessary for diabetic patients who have no alternatives; this has been described in the literature using the product neutral protamine Hagedorn. One protocol successfully describes a starting dose of 0.001 units intradermally, doubling every 20 to 30 minutes until a dose of 0.1 unit is reached. The protocol then continues with subcutaneous injections until they reach the goal dose of 4 units.[752]

Coagulation factors (by Craig D. Platt, MD, PhD)

General. The use of coagulation factors is the cornerstone of treatment for hemophilia A (deficiency of factor VIII), hemophilia B (deficiency of factor IX), and type III von Willebrand disease (vWD) (the most severe form of vWD).[753,754]

TABLE LXXXIV. Recommended immediate hypersensitivity testing for vWF-containing products and FVIII[762]

Product	SPT	IDT 1	IDT 2
Wilate	vWF 100 IU/mL, FVIII 100 IU/mL	vWF 10 IU/mL, FVIII 10 IU/mL	vWF 100 IU/mL, FVIII 100 IU/mL
Humate P	vWF 120 IU/mL, FVIII 50 IU/mL	vWF 12 IU/mL, FVIII 5 IU/mL	vWF 120 IU/mL, FVIII 50 IU/mL
Helixate	300 IU/mL	30 IU/mL	300 IU/mL
Advate	300 IU/mL	30 IU/mL	300 IU/mL
Xytha	300 IU/mL	30 IU/mL	300 IU/mL
Monoclate	300 IU/mL	30 IU/mL	300 IU/mL

FVIII, Factor VIII; *vWF*, von Willebrand factor.

TABLE LXXXV. Recommended immediate hypersensitivity testing for factor IX[764]

Product	SPT	IDT 1	IDT 2
Mononine	100 IU/mL	1 IU/mL	10 IU/mL
Monoclate	100 IU/mL	1 IU/mL	10 IU/mL

IU, International unit.

TABLE LXXXVI. Desensitization protocol to factor IX*

Day	Dose (units/kg)	Cumulative dose (units/kg)	Method	Interval from infusion of previous dose
Day 1	0.01	0.1	Slow IV push	0 min
	0.02	0.3	Slow IV push	10 min
	0.04	0.7	Slow IV push	10 min
	0.08	0.15	Slow IV push	10 min
	0.1	0.25	Slow IV push	10 min
	0.2	0.45	Slow IV push	20 min
	0.4	0.85	Slow IV push	20 min
	0.8	1.65	Slow IV push	20 min
	1.5	3.15	Slow IV push	20 min
	3.0	6.15	Continuous infusion over 30 min	—
	6.0	12.15	Continuous infusion over 30 min	—
	8.0	20.15	Continuous infusion over 30 min	—
	9.0	29.15	Continuous infusion over 60 min	—
	11.0	40.15	Continuous infusion over 60 min	—
	12.0	52.15	Continuous infusion over 60 min	—
	14.0	66.15	Continuous infusion over 60 min	—
	16.0	82.15	Continuous infusion over 60 min	—
	18.0	100.15	Continuous infusion over 60 min	—
Day 2	100	100	Continuous infusion over 10 h	—
Day 3	100	100	Continuous infusion over 8 h	—
Day 4	100	100	Continuous infusion over 6 h	—
Day 5	100	100	Continuous infusion over 4 h	—
Day 6	100	100	Continuous infusion over 2 h	—
Day 7	100	100	Continuous infusion over 1 h	—
Day 8	100	100	Continuous infusion over 30 min	—

*This protocol was devised and used successfully, given severe persistent urticaria with a standard 12-step approach.

Unfortunately, 2 major complications can prevent optimal therapy in a subset of patients. First, inhibitory alloantibodies (predominantly of the isotype IgG) to the exogenously supplied coagulation factors can develop.[755,756] Such inhibitors substantially increase the risk of morbidity and mortality due to incomplete hemostasis. Second, acute hypersensitivity reactions, often with features of anaphylaxis, can occur with infusions.[755,756] In some cases, patients simultaneously develop inhibitors and hypersensitivity reactions, a challenging clinical scenario that significantly limits treatment options.[755,756]

Major symptoms of hypersensitivity. Symptoms of anaphylaxis associated with factor infusion have been most commonly described in patients with hemophilia B. Although only 3% to 5% of patients develop inhibitory antibodies, the development of such antibodies is a major risk factor for anaphylaxis.[755-757] Warrier et al[757] reviewed 18 such cases. The clinical manifestations of hypersensitivity reactions were (listed from most to least frequent) rash, bronchospasm, angioedema, emesis, restlessness, cough, hypotension, and syncope.[757] Patients with complete factor IX gene deletion have been shown to

TABLE LXXXVII. Twelve-step desensitization protocol to wilate*

Full therapeutic dose:	435 IU daily
Premedication	Diphenhydramine†

A. Prepared solutions

Solution	mL/bag	IU/bag	IU/mL
1	250	4.35	0.017
2	250	43.5	0.174
3	250	431.6	1.726

B. Desensitization

Step	Solution	Rate (mL/h)	Time (min)	Dose (IU)	Cumulative dose (IU)
1	1	2	15	0.009	0.009
2	1	5	15	0.022	0.031
3	1	10	15	0.044	0.074
4	1	20	15	0.087	0.161
5	2	5	15	0.218	0.379
6	2	10	15	0.435	0.814
7	2	20	15	0.870	1.684
8	2	40	15	1.740	3.424
9	3	10	15	4.316	7.739
10	3	20	15	8.632	16.371
11	3	40	15	17.263	33.634
12	3	75	186	401.37	435.000
Total time			351 min		

IU, International unit.
*The total IU dose injected is more than the final dose because solutions 1 and 2 are not completely infused.
†Oral dose of 1 mg/kg, 1 h before start of desensitization and 1 h before each subsequent dose.

be at the greatest risk of developing inhibitors and anaphylaxis.[757] There does not seem to be a single common mechanism for anaphylaxis, because the development of IgG_1, IgG_4, and IgE to factor IX has been described.[756]

Although up to 30% of patients with hemophilia A receiving factor VIII replacement develop inhibitors, anaphylaxis is a very rare complication.[756] Unlike in hemophilia B, there does not appear to be a correlation with anaphylaxis and the development of inhibitory antibodies.[756] Published reports of such reactions have included respiratory distress, hypotension, and diffuse urticaria or erythroderma.[758,759] In several cases, allergic reactions to factor VIII infusions have been presumed to be triggered by concentrate components other than the factor VIII itself.[759,760]

Inhibitory antibodies develop in approximately 10% of patients with type III vWD.[761,762] Anaphylaxis has been reported in a number of these patients, though good estimates of the incidence of anaphylaxis in patients with inhibitors is lacking.[719,756,761-763] Two siblings with type III vWD have been recently described, one of whom developed shortness of breath, urticaria, tachycardia, and mild hypotension. His sibling's symptoms were limited to respiratory distress and back pain.[762]

Diagnosis. Skin testing protocols have been described for factor XIII (Table LXXXIV), factor IX (Table LXXXV), and von Willebrand factor (Table LXXXIV).[762,764,765] However, in most cases, IgG alloantibodies are responsible for the reactions and these antibodies are not detected on such testing.[755,756] Patients with hemophilia B and vWD with documented inhibitory antibodies should be considered at risk for anaphylaxis with factor infusions.[755,756] Patients with hemophilia A, even those with high levels of inhibitors, are not considered at elevated risk of an acute hypersensitivity reaction.[755,756]

Management. The use of bypassing agents recombinant factor VII activated and activated prothrombin complex concentrates including factor VIII inhibitor bypassing activity has been described for acute bleeding episodes in patients with hemophilia A, hemophilia B, and vWD.[766,767] Desensitization protocols have been published for all 3 disorders as well (Tables LXXXVI and LXXXVII).[762-765] For patients with inhibitors to these factors, such protocols can be the first step of an immune tolerance induction protocol.[762,768] It is important to note that nephrotic syndrome is a relatively common complication of immune tolerance induction in patients with hemophilia B and therefore episodic control with recombinant factor VII activated rather than immune tolerance induction should be strongly considered.[768]

OTHER DRUGS

Radiographic contrast media (by Knut Brockow, MD)

General. Adverse reactions to iodinated radiocontrast media (RCM) may be either chemotoxic (eg, cardiotoxicity, neurotoxicity, and nephrotoxicity) or due to hypersensitivity.[769] Hypersensitivity reactions manifest either immediately (<1 hour of administration) or are nonimmediate responses (>1 hour). Immediate hypersensitivity reactions present with anaphylaxis, and nonimmediate reactions predominantly are exanthems.[769] The pathogenesis is normally related to the molecular RCM structure and not to iodine or to seafood allergy.[770] There is increasing evidence that some of these reactions may be immunologic and that allergy tests may help to identify agents that may be tolerated.[769,771] Mild immediate

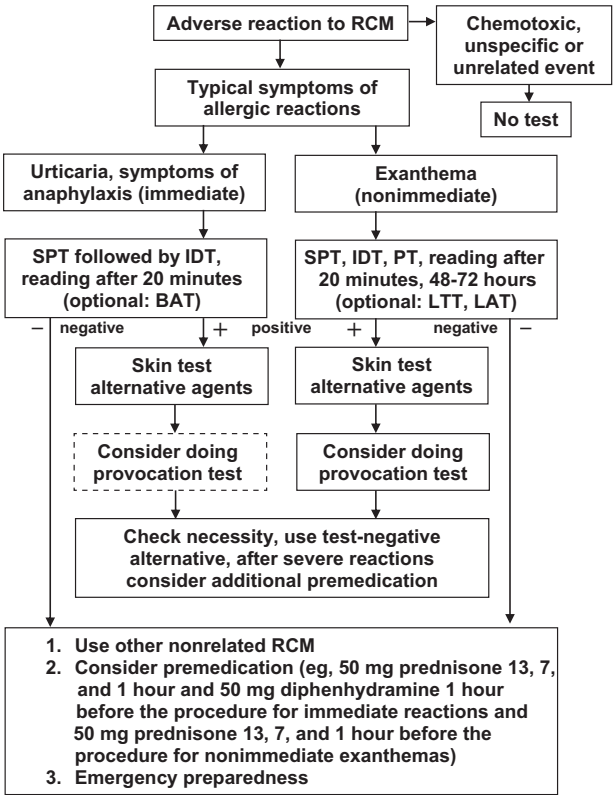

FIGURE 8. Test procedure in RCM hypersensitivity.[769] *LAT,* lymphocyte activation test; *LTT,* lymphocyte transformation test.

hypersensitivity reactions, such as urticaria and pruritus, have been reported to occur in 0.7% to 3.1% of patients receiving modern nonionic RCM, whereas severe life-threatening reactions occur in 0.02% to 0.04% of patients, and fatal hypersensitivity in 1 to 3 per 100,000 RCM administrations.[769] The frequency of reported nonimmediate exanthems varies greatly and has been reported to affect about 1% to 3% of RCM-exposed patients.[769]

Major symptoms. Immediate RCM hypersensitivity reactions manifest with symptoms of anaphylaxis.[771] Pruritus and urticaria with or without angioedema are most common. Gastrointestinal symptoms such as nausea, vomiting, abdominal pain, and diarrhea may occur. Reactions may involve the respiratory and cardiovascular systems and present with dyspnea, bronchospasm, and/or a sudden drop in blood pressure. Hypotension may be associated with loss of consciousness (anaphylactic shock). The onset of immediate hypersensitivity reactions is within 5 minutes after injection in about 70% of reactions[771]; 96% of severe or fatal reactions manifest within 20 minutes.

Nonimmediate RCM hypersensitivity reactions are usually mild to moderate in severity and are self-limiting. The typical clinical manifestation is a maculopapular exanthem occurring within a few hours to several days after the RCM administration.[771] Uncommon skin reactions including erythema, urticaria, angioedema, fixed drug eruption, erythema multiforme, SJS, TEN, and papulopustular eruptions have been described.[771]

Diagnosis. For immediate hypersensitivity reactions, anaphylaxis may be confirmed by obtaining blood samples for histamine analysis drawn immediately, or for tryptase ideally drawn 1 to 2 hours after the onset of symptoms. The further allergy workup should be performed within 6 months after the reaction for best test results (Figure 8).[771] It consists of a SPT with undiluted RCM followed by IDT with RCM (300-320 mg/mL) diluted 10-fold in sterile saline and reading after 20 minutes (Table LXXXVIII).[771] In case of a positive reaction, a panel of several different RCM should be tested. There is no commercial assay for RCM-specific IgE antibodies. Increased basophil activation to RCM has been described, but the reliability of this or other *in vitro* tests has not yet been sufficiently established. Several studies from Europe and Asia have shown that skin testing may be helpful in patients with past hypersensitivity reactions to RCM. Skin tests with RCM will give positive results only in a minority (∼10%-25%) of immediate and 30% to 70% of nonimmediate reactions with clinical pictures typical for drug hypersensitivity reactions.[771,772]

For nonimmediate exanthems, it is recommended to use SPT and patch tests with undiluted RCM and IDTs with 10-fold diluted products in physiologic saline with delayed readings after 48 and 72 hours (in case of local pruritus or erythematous plaques also at additional time points; Table LXXXVIII).[771] RCM-related T-cell activity may additionally be assessed *in vitro* by lymphocyte transformation test and by lymphocyte activation test, although their sensitivity and specificity remain unknown, and these tests are not commercially available.

Drug challenge has not been generally recommended because intravenous applications of as low as 1 mL RCM have anecdotally led to severe anaphylaxis. However, evidence is increasing that, in experienced centers, challenge tests can be performed to confirm results of skin tests.[773]

Graded drug challenge tests have been recommended to confirm negative skin test results, for example, 1/10 of the full dose on day 1, $^1/_2$ of the full dose on day 2, and the full dose on day 3 at the radiology department, because a negative skin test result does indicate, but does not necessarily guarantee, tolerance.[769] At this time there is inadequate published experience in the pediatric population; therefore, the approach to hypersensitivity to RCM in children has been modeled from the one used for adults.

Management. Patients with previous hypersensitivity reactions to RCM are at risk for developing new reactions on reexposure.[769] If such patients need another contrasted examination, the culprit preparation should be avoided, particularly if there is a history of severe reactions. In those with positive skin test reaction to the culprit, cross-reactivity to other RCMs is common.[772] The risk of RCM cross-reactivity to different RCMs appears to be related to the structure of the culprit. Three different groups of RCM have been proposed, with frequent reactions within groups and scarce skin test positivity among RCMs of different groups.[772] In case of a positive reaction, a skin test−negative product should be identified. The preventive value for the selection of an alternative RCM by skin test still has to be further confirmed. The benefit is limited to those patients with positive skin tests to RCM. In the United States, skin testing after immediate reactions to RCM is not considered standard of care; however, the role of skin tests in the evaluation is evolving. In 1 study, however, the negative predictive value of reapplication of RCM in combination with skin tests was reported to be high.[773] A fractionated challenge test may be considered in nonimmediate exanthems. In patients with negative skin test result or in whom skin tests are not performed, the use of premedication with antihistamines and/or glucocorticoids is no longer recommended. The anaphylaxis 2020 practice

TABLE LXXXVIII. Skin test concentrations for radiocontrast media*

Test	Concentration*	Readings	
		Immediate reaction	Nonimmediate reaction
Skin prick test	Undiluted	20 min	20 min, 48 h, 72 h†
Intradermal test	1/10 diluted	20 min	20 min, 48 h, 72 h†
Patch test	Undiluted		20 min, 48 h, 72 h†

*Radiocontrast media with an iodine concentration of 300-320 mg/mL.
†If the patient notices a positive reaction (pruritus, erythema) at the skin test site at other time points, additional readings may be performed (eg, after 24 h or 96 h).

TABLE LXXXIX. Recommended immediate hypersensitivity testing for corticosteroids and excipients*[777-781,792,802,804]

Corticosteroid	SPT dilutions (mg/mL)	IDT dilutions (mg/mL)	References
Betamethasone sodium phosphate	4-6	0.006	SPT: Asakawa, Figueredo, Venturini, Rachid
		0.06	IDT: Figueredo, Rachid
		0.6	
		4-6	
Betamethasone acetate	6	6	SPT: Mace IDT: Montoro
Budesonide	0.25	0.0025	SPT: Venturini
		0.025	IDT: Venturini
Dexamethasone sodium phosphate	4	0.004	SPT: Mace, Venturini, Rachid
		0.04	IDT: Rachid, Baker, Venturini
		0.4	
		4	
Hydrocortisone sodium succinate	10-100	0.01-1	SPT: Figueredo, Venturini, Rachid
		0.1-10	IDT: Rachid, Venturini, Montoro
		10-25	
Methylprednisolone acetate	40	0.4	ST: Mace, Venturini
		4	IDT: Baker, Venturini
Methylprednisolone sodium succinate	10-40	0.01	ST: Mace, Rachid
		0.1-0.4	IDT: Baker, Rachid
		4-10	
Prednisone	3-30	No IDT	Venturini, Rachid
Prednisolone	3-10	No IDT	Venturini, Rachid
Triamcinolone acetonide	10-40	0.01	SPT: Venturini, Rachid
		0.1-0.4	IDT: Baker, Venturini, Montoro, Rachid
		1-4	
		10-40	
Polyethylene glycol†	10 (1:100)	0.1 (1:10,000)	SPT: Sohy
	100 (1:10)	1 (1:1,000)	
		10 (1:100)	
Carboxymethylcellulose†	5	0.005	Venturini
		0.05	

*Dilutions adapted from cited publications.
†Dilutions based on literature and not personal experience.

parameter update performed a systematic review and Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) analysis and suggested against premedication to prevent anaphylaxis in patients with prior radiocontrast HSRs when readministration of a low- or iso-osmolar, nonionic RCM agent is required.[774] This was a conditional recommendation with the certainty rating of evidence as being very low. Therefore premedication may be considered in clinical circumstances associated with a high level of perceived risk of anaphylaxis or comorbidities associated with greater anaphylaxis fatality risk (such as underlying cardiovascular disease, use of beta-blockers, or prior severe anaphylaxis), although evidence is lacking to clearly support this practice and breakthrough reactions may still occur. Corticosteroids (eg, 50 mg prednisone 13, 7, and 1 hour before the procedure) and H_1 (eg, 50 mg diphenhydramine 1 hour before the procedure) $\pm$ H_2 antihistamines are the most frequently recommended premedication agents. Physicians dealing with these patients should not rely on the efficacy of premedication.

Corticosteroids (by Iris Otani, MD, and Rima Rachid, MD)

Background. Corticosteroids are used in the treatment of several conditions, including allergic conditions, malignancy, autoimmunity, and transplantation. Immediate

TABLE XC. Previously published desensitization protocol for methylprednisolone[807]

Bag			Volume per bag (mL)			Concentration (mg/mL)
1			250			0.040
2			250			0.400
3			250			3.969
Step	**Bag**	**Rate (mL/h)**	**Time (min)**	**Administered volume (mL)**	**Administered dose (mg)**	**Cumulative dose (mg)**
1	1	2	15	0.5	0.02	0.02
2	1	5	15	1.25	0.05	0.07
3	1	10	15	2.5	0.1	0.17
4	1	20	15	5	0.2	0.37
5	2	5	15	1.25	0.5	0.87
6	2	10	15	2.5	1	1.87
7	2	20	15	5	2	3.87
8	2	40	15	10	4	7.87
9	3	10	15	2.5	9.921	17.791
10	3	20	15	5	19.843	37.634
11	3	40	15	10	39.685	77.319
12	3	80	174.375	232.5	922.681	1000

hypersensitivity reactions to corticosteroids are overall rare. The exact incidence is unknown, but hypersensitivity reactions to corticosteroids have been reported with an estimated prevalence of 0.1% to 0.3%.

Clinical presentation. Most immediate hypersensitivity reactions to corticosteroids occur within an hour of administration. Symptoms may include 1 or more of the following: urticaria, angioedema, wheezing, bronchospasm, nausea, vomiting, hypotension, or even cardiovascular collapse.[775,776] Recognition of corticosteroids as the culprit for these reactions is sometimes challenging, because they are often used to treat conditions that may lead to similar symptoms, such as allergic reactions, status asthmaticus, anaphylaxis, or shock. Hence, hypersensitivity reactions to corticosteroids may go unrecognized and patients may develop more than 1 reaction before this diagnosis is suspected. It is not clear whether some types of corticosteroids are more prone to causing hypersensitivity reactions than others, or whether the likelihood of reactions is related to the frequency of administration of specific corticosteroids. In a recent review of the literature from 2004 to 2014, 120 hypersensitivity reactions to corticosteroids were reported in 106 patients. Methylprednisolone was implicated in 41% of all types of reactions, followed by prednisolone (20%), triamcinolone (14%), and hydrocortisone (10%).[775,776] Reactions occur most commonly after intravenous (44% of cases) and oral (26%) administration, though reports of reactions after intra-articular, ophthalmic, and topical administration have also been published.[775-777]

Diagnosis and management of immediate hypersensitivity reactions. Identification of an alternative corticosteroid for future use is possible in most cases with skin prick and intradermal testing at nonirritating concentrations (Table LXXXIX) and graded challenge.[775,776,778-781] Whenever possible, testing should be performed with a preservative-free corticosteroid, in addition to preservative testing if needed. Negative skin test results should be confirmed with drug challenge.[782-800] Cross-reactivity patterns based on structural characteristics have not been clearly established for immediate hypersensitivity reactions as they have been for delayed reactions as described by Coopman et al.[801-804] Some reports suggested that hydrocortisone is more cross-reactive with methylprednisolone than with halogenated corticosteroids such as dexamethasone and betamethasone, whereas others did not find a definite pattern of cross-reactivity based on the history and skin and intradermal testing.[802,805,806]

Hydrophobic corticosteroids are sometimes chemically bonded to an ester such as sodium succinate or sodium phosphate to transform them into soluble injectable products. Immediate hypersensitivity reactions have been reported to the succinate ester component of the corticosteroids.[784,786,804,807-811] Hence, when evaluating a reaction that is thought to be secondary to esterified corticosteroids, it is recommended to include the suspected corticosteroids in the skin and intradermal testing, and, in addition, the same corticosteroids without the ester component or with a different ester.

Immediate hypersensitivity reactions can also occur because of excipients or preservatives in a corticosteroid preparation. Sensitivities to lactose, carboxymethylcellulose, polyethylene glycol, and hexylene glycol have been reported.[782,783,785,787,789-793,803,812-816] When preservatives or excipients are present in the corticosteroid preparation, skin testing with these agents can be considered. Skin testing with milk proteins can be considered in patients with milk allergy reacting to lactose-containing corticosteroid preparations.

Desensitization to methylprednisolone has been successfully performed and is an option when an alternative therapeutic agent cannot be identified (Table XC).[807]

Contact dermatitis (delayed hypersensitivity) to topical corticosteroids

Background. Contact dermatitis to topical corticosteroids has been reported with a frequency of 0.5% to 5%.[788] Contact dermatitis to corticosteroids occurs more frequently in women (3:1 women to men), and among the following occupations: housewife (18%), office work (17%), retired (7%), housekeeping (6%), education (5%), student (5%), and health care (4%).[795]

Diagnosis and management. Patch testing is the standard for diagnosing contact dermatitis.[797] A combination of

TABLE XCI. Observed cross-reactivity patterns within corticosteroid groupings based on the classification by Coopman et al[801] and modified by Matura and Goossens[788]

Group	Structure	Cross-reactivity
A—Hydrocortisone type • Hydrocortisone • Methylprednisolone • Prednisolone	Short-chain ester or thioester on C_{21}	Within group With budesonide-(S)-isomer and group D2 corticosteroids
B—Triamcinolone acetonide type • Desonide • Fluocinolone • Tramcinolone	C_{16}, C_{17}-*cis*-ketal or -diol	Within group Budesonide-(S)-isomer cross-reacts with group A and D2 corticosteroids
C—Betamethasone type	C_{16}-methyl substitution	
C1 • Betamethasone • Dexamethasone • Desoximetasone	Nonesterified	Betamethasone and/or dexamethasone and group B
C2 • Diflucortolone • Fluocortolone • Clocortolone	Stable esters (-valerate, -propionate, -diflucortolone valerate, -flumethasone pivalate)	No significant cross-reactivity pattern observed
D—Hydrocortisone-17-butyrate type	Long-chain ester at C_{17} or C_{17} and C_{21} with or without C_{16}-methyl substitution	
D1 • Clobetasol-17-propionate • Betamethasone dipropionate • Mometasone furoate • Aclometasone dipropionate	C_{16} methyl substitution on B ring	Rare cross-reactivity between aclomethasone dipropionate and group A, budesonide, group D2
D2 • Hydrocortisone-17-butyrate • Hydrocortisone valerate	Lacks long-chain ester and methyl substitution Lipophilic prodrugs that penetrate skin easily	Within group With group A corticosteroids With budesonide-(S)-isomer

tixocortol-21-pivalate and budesonide included in the thin-layer rapid use epicutaneous test can identify 91.3% of corticosteroid-sensitivity patients.[796] Supplemental patch testing is needed to identify the culprit corticosteroid in the remaining patients. Baeck et al[795] provide comprehensive vehicle and concentration recommendations for corticosteroid patch testing in their review. Cross-reactivity patterns within modified Coopman classification groups have been observed for delayed reactions (Table XCI). For patients with positive reactions to tixocortol-21-pivalate or budesonide on thin-layer rapid use epicutaneous test, consideration of cross-reactivity patterns and supplemental patch testing can help identify corticosteroids that can be tolerated for future therapeutic use.

Vehicles used for topical corticosteroid preparations can also cause irritation or contact dermatitis. Parabens, formaldehyde-releasing preservatives (quaternium-15), isothiazolinones, lanolin, ethylenediamine, sorbitan sesquioleate, fragrance, and propylene glycol are all known contact allergens commonly used in topical corticosteroid preparations.[794,798-800,817-819] The thin-layer rapid use epicutaneous test includes all these additives except for propylene glycol, for which testing can be performed with 30% aqueous solutions, and sorbitan sesquioleate, for which testing can be performed with 20% petrolatum preparations.[820,821]

Proton pump inhibitors (by Anna Wolfson, MD)

General. Proton pump inhibitors (PPIs) are widely used inhibitors of gastric acid secretion. PPIs are generally well tolerated, with a 1% to 2% risk of minor adverse reactions with rare reports of serious adverse events.[822] Hypersensitivity is also rarely described.[823-825]

PPIs are modified benzimidazoles that contain a pyridine ring and unique side-chain substitutions. Omeprazole and pantoprazole have a methoxy and a difluoromethoxy chain in their benzimidazole rings, respectively, whereas lansoprazole and rabeprazole have a trifluoroethoxy and methoxypropoxy chain in their pyridine rings, respectively. Multiple case reports have described possible cross-reactivity among PPIs, based on the underlying structural similarity and confirmed by skin testing.[823,826-828] Three patterns of cross-reactivity are described on the basis of combining the data from the most recent literature.[829]

1. Hypersensitivity to omeprazole showed cross-reactivity with all other PPIs.[825,828]
2. Hypersensitivity to omeprazole showed cross-reactivity with pantoprazole, or with pantoprazole and esomeprazole or rabeprazole, but not with lansoprazole.[824-826,828]
3. Hypersensitivity to lansoprazole showed cross-reactivity with 1 (omeprazole, pantoprazole, rabeprazole, esomeprazole) but not with any of the other PPIs.[824,828,830,831]

Major symptoms of hypersensitivity. Among the PPIs, lansoprazole, followed by omeprazole, is most frequently implicated as the cause of immediate hypersensitivity.[823,824] IgE-mediated reactions are most commonly reported, accounting for 86% of all hypersensitivity reactions in a recent review of 118 cases.[823] In this same review, the clinical manifestations of hypersensitivity reactions were (listed from most to least frequent) urticaria, generalized itching or pruritus, angioedema, hypotension, skin rash other than urticaria, erythema, and dyspnea or shortness of breath.[823] The clinician should keep in mind that,

TABLE XCII. Recommended immediate hypersensitivity testing for PPIs[823,824]

	Bose et al[823]		Kepil Ozdemir et al[824]	
PPI	SPT dilutions (mg/mL)	IDT dilutions (mg/mL)*	SPT dilutions (mg/mL)	IDT dilutions (mg/mL)*
Omeprazole	40	0.04	0.4	0.004
		0.4	4	0.04
		4	20	0.4
Esomeprazole	40	0.04	0.8	0.008
		0.4	8	0.08
		4	20	0.8
Lansoprazole	30	0.03	30	None
		0.3		
		3		
Pantoprazole	40	0.04	0.4	0.004
		0.4	4	0.04
		4	40	0.4
Rabeprazole	20	0.02	20	None
		0.2		
		2		

*Intradermal testing should only be performed using injectable intravenous preparations of PPIs.

TABLE XCIII. Oral desensitization protocol for omeprazole*[839]

Time (h)	Concentration (mg/mL)	Dose (mL)	Dose (mg)	Cumulative dose (mg)
0:20	0.002	0.5	0.001	0.001
0:40	0.002	1	0.002	0.003
1:00	0.002	2	0.004	0.007
1:20	0.002	4	0.008	0.015
1:40	0.02	0.5	0.01	0.025
2:00	0.02	1	0.02	0.045
2:20	0.02	2	0.04	0.085
2:40	0.02	4	0.08	0.165
3:00	0.2	0.5	0.1	0.265
3:20	0.2	1	0.2	0.465
3:40	0.2	2	0.4	0.865
4:00	0.2	4	0.8	1.665
4:20	2	0.5	1	2.665
4:40	2	1	2	4.665
5:00	2	2	4	8.665
5:20	2	4	8	16.665
5:40	2	8	16	32.665

*Omeprazole granules were dissolved into bicarbonate solution to create serial dilutions.

because many of the drugs are delayed release preparations, patients may present with hypersensitivity symptoms 2 to 3 hours after ingestion as opposed to the classic teaching of 1 hour.[823]

The remaining 14% of cases were non−IgE-mediated and included 1 case of DRESS to esomeprazole (a subsequent case reported DRESS to omeprazole[832]), 1 case of TEN to lansoprazole, 1 case of hypersensitivity vasculitis, and 5 cases of contact dermatitis (3 of which were occupational exposures, 1 to lansoprazole and 2 to omeprazole).[823] A subsequent large case series of 96 cases of occupational sensitization to omeprazole identified 36 patients with evidence of sensitization to omeprazole based on patch testing and lymphocyte transformation test.[833] Acute interstitial nephritis has been well described with PPI use.[834] Subacute cutaneous lupus erythematosus has also been described.[835]

Diagnosis. The validity of skin testing for the evaluation of immediate hypersensitivity to PPIs has been studied in a prospective analysis by Kepil Ozdemir et al,[824] who reported a sensitivity of 58.8%, specificity of 100%, negative predictive value of 70.8%, and positive predictive value of 100%. Their skin testing protocol is outlined in Table XCII as well as the protocol proposed by Bose et al,[823] which is based on a broader literature review. In clinical experience, cross-reactivity among all the PPIs can be seen.[836] Unfortunately, the low negative predictive value of skin testing means that this is often observed during the oral challenge. The BAT, when used in conjunction with skin testing, has been described as being a useful guide for whether oral challenge should be performed.[837]

Patch testing has been used in cases of suspected delayed hypersensitivity. Ghatan et al[833] used an omeprazole sodium salt

TABLE XCIV. Rapid 2-d oral desensitization protocol for immediate hypersensitivity to allopurinol

Interval (min)	Solution*	Volume (mL)	Dose (mg)
Day 1	B	0.25	0.05
30	B	0.5	0.1
30	B	1	0.2
30	B	2.5	0.5
30	B	5	1
30	A	2.5	5
30	A	5	10
30	A	12.5	25
30	Half 100-mg tablet	—	50
30	100-mg tablet	—	100
Day 2	100-mg tablet	—	100
60	Two 100-mg tablets	—	200

*Solution A: Crush 2 tablets of 100 mg allopurinol into a volume of 100 mL diluent (Ora-Plus/Ora-Sweet 1:1) to a final concentration of 2 mg/mL; Solution B: 1:10 dilution of solution A to a final concentration 0.2 mg/mL.

TABLE XCV. Twenty-eight-day allopurinol desensitization protocol for delayed hypersensitivity*

Days	Daily dose	Allopurinol administration instructions (by mouth)
1-3	50 μg	0.25 mL of suspension A
4-6	100 μg	0.5 mL of suspension A
7-9	200 μg	1 mL of suspension A
10-12	500 μg	2.5 mL ($^1/_2$ tsp) of suspension A
Then change to suspension B		
13-15	1 mg	1 mL of suspension B
16-18	5 mg	5 mL (1 tsp) of suspension B
19-21	10 mg	10 mL (2 tsp) of suspension B
22-24	25 mg	$^1/_4$ of a 100-mg tablet or 25 mL (5 tsp) of suspension B
25-27	50 mg	$^1/_2$ of a 100-mg tablet
28 and on	100 mg	1 full 100-mg tablet

tsp, Teaspoon.
*Suspension A: Allopurinol 0.2 mg/1 mL (100 mL); Suspension B: allopurinol 1 mg/1 mL (200 mL).

in saline solution at 0.1%, 0.5%, and 1% for patch testing. In the case of severe, life-threatening delayed reactions to PPIs, such as DRESS and TEN, reexposure to a suspected culprit for testing purposes must be performed with extreme caution and empiric avoidance is recommended.

Management. Many patients with hypersensitivity to a PPI can tolerate an alternative PPI, and skin testing (usually to the culprit PPI, and to at least 1 other PPI) followed by oral challenge can identify candidate alternates.[838] Finally, a successful desensitization protocol to omeprazole in the context of immediate IgE-mediated hypersensitivity has been published (Table XCIII).[839]

Allopurinol (by Alberta L. Wang, MD)

General. Allopurinol is the primary therapeutic agent used for the treatment of gout and hyperuricemia. Most allopurinol hypersensitivity reactions are delayed, with a median time of onset of 3 weeks, but reactions have been reported to occur years after initiation of therapy.[840] Rash is the most common manifestation of allopurinol hypersensitivity, with an overall incidence of approximately 2%.[841] SCARs to allopurinol, including DRESS, SJS, and TEN, are rare but have a high associated mortality of up to 27%.[842]

Allopurinol is rapidly metabolized by xanthine oxidase to oxypurinol, which has a half-life of 23 hours, and is excreted by the kidney. Allopurinol hypersensitivity is primarily mediated by $CD4^+$ and $CD8^+$ T-cell responses to oxypurinol.[843] The risk of hypersensitivity reaction is increased by factors that decrease oxypurinol excretion, including impaired kidney function and concurrent diuretic use. The HLA-B*58:01 allele is also associated with an increased risk for allopurinol hypersensitivity.[844] There is an increased prevalence of allopurinol hypersensitivity in Asian subpopulations, which has been correlated with higher HLA-B*58:01 allele frequencies. HLA-B*58:01 screening is recommended for patients of Korean ethnicity with chronic kidney disease stage 3 or worse and patients of Han Chinese or Thai ethnicity irrespective of renal function before initiation of allopurinol.[845]

Major symptoms of hypersensitivity. The most common hypersensitivity reaction to allopurinol is a maculopapular exanthem. The incidence of SCARs, including DRESS, SJS, and TEN, is rare (~0.1%). However, allopurinol users have a 10 times higher relative risk of a SCAR compared with nonusers, and allopurinol is a common cause of SJS and TEN.[846,847] In addition, systemic hypersensitivity with acute interstitial nephritis has been described in case reports.[848,849]

TABLE XCVI. Sixteen-day allopurinol desensitization protocol for delayed hypersensitivity*

Day	Solution	Amount	Dose (mg)
1	A	1 mL	0.3
2	A	2 mL	0.6
3	A	4 mL	1.2
4	A	8 mL	2.4
5	A	10 mL	3
6	B	3 mL	18
7	B	6 mL	36
8	B	10 mL	60
9	100-mg tablet	3/4 tablet	75
10	100-mg tablet	1 tablet	100
11	100-mg tablet	1 1/4 tablet	125
12	100-mg tablet	1 1/2 tablet	150
13	100-mg tablet	1 3/4 tablet	175
14	100-mg tablet	2 1/4 tablet	225
15	100-mg tablet	2 1/2 tablet	250
16	300-mg tablet	1 tablet	300

*Source solution: 150-mg allopurinol tablet in 50 mL 5% dextrose (final concentration 3 mg/mL); Solution A: 1:10 source solution (0.3 mg/mL); Solution B: 300-mg allopurinol tablet in 50 mL 5% dextrose (final concentration 6 mg/mL).

TABLE XCVII. Seventy-eight-day allopurinol desensitization protocol for delayed hypersensitivity

Daily dose	Concentration/tablet	Amount	Days
10 μg	1 mg/5 mL	0.05 mL	1-7
25 μg	1 mg/5 mL	0.12 mL	8-14
50 μg	1 mg/5 mL	0.25 mL	5-21
100 μg	1 mg/5 mL	0.5 mL	22-28
200 μg	1 mg/5 mL	1 mL	29-35
500 μg	1 mg/5 mL	2.5 mL	36-42
1 mg	1 mg/5 mL	5 mL	43-49
5 mg	10 mg/5 mL	2.5 mL	50-56
10 mg	10 mg/5 mL	5 mL	57-63
25 mg	10 mg/5 mL	12.5 mL	64-70
50 mg	100-mg tablet	1/2 tablet	71-77
100 mg	100-mg tablet	1 tablet	≥78

Diagnosis. Diagnosis is based on clinical history and symptom recognition, in particular, the temporal relationship between allopurinol initiation and symptom onset. Allopurinol skin testing concentrations for IgE-mediated reactions are not standardized or validated. Intradermal skin testing with 0.1 μg of allopurinol has been reported with negative result in a patient who presented with IgE-mediated symptoms.[850] Patch testing with allopurinol has also been reported with low sensitivity.[842] Drug patch testing for systemic hypersensitivity reactions is not standardized and the predictive value is unknown.[13]

Management. The mainstay of treatment is cessation of allopurinol and supportive care. For patients with a continued indication for urate-lowering therapy, an alternative agent should be considered. If allopurinol treatment is necessary and the initial hypersensitivity reaction was not severe, desensitization can be performed on an individual basis weighing the risks and benefits of treatment. The type and severity of the initial reaction, patient comorbidity, and urgency of treatment should be considered when choosing a desensitization protocol.

In patients with a history of IgE-mediated reaction to allopurinol, case reports have described success with rapid intravenous desensitization.[851] In addition, a rapid 2-day oral desensitization protocol with a target dose of 200 mg has been published (Table XCIV).[852]

Published desensitization protocols for DHRs range from 16 to 78 days.[13,853,854] The standard 28-day oral desensitization protocol (Table XCV) is generally well tolerated.[853] The 28-day protocol balances the reduction of breakthrough reactions during desensitization, such as fever and rash, and the length of desensitization. The 28-day protocol reaches a target dose of 100 mg/d. For a target dose higher than this, one can continue to increase the dose up to 2-fold every 3 days as tolerated. The protocol can be modified with dosage adjustments and by lengthening the time between steps if breakthrough reactions occur. In patients who need allopurinol more urgently, a shorter 16-day oral desensitization protocol that reaches a target dose of 300 mg can be used (Table XCVI).[853] A longer 78-day oral desensitization protocol is recommended for high-risk patients who are frail or elderly with multiple medical comorbidities,

TABLE XCVIII. Pharmacogenomics of severe immunologically mediated adverse reactions associated with antiepileptic drugs[353,868]

Drug	Clinical phenotype	Genetic association	Population
Carbamazepine	SJS/TEN	HLA-B*15:02 HLA-B*15:21*	Han Chinese, Thai, Malaysian, Hindu Indian
		HLA-B*15:11	Korean, Japanese
		HLA-B*15:18	Japanese
		HLA-B*59:01	Japanese
		HLA-A*31:01	Northern European
		HLA-A*31:01	Japanese, Korean
	DRESS	HLA-A*31:01	European, Japanese, Chinese
Oxcarbazepine	SJS/TEN	HLA-B*15:02, HLA-B*15:18	Han Chinese
Phenytoin	SJS/TEN	HLA-B*15:02	Han Chinese, Thai
		HLA-B*13:01	Han Chinese
		HLA-C*08:01/DRB1*16:02	Han Chinese
	SJS/TEN/DRESS	CYP2C9*3	Taiwan, Japan, Malaysia
Phenobarbital	SJS/TEN	?HLA-B*51:01	Japan
Lamotrigine	SJS/TEN	HLA-B*15:02 HLA-B38 HLA-A*68:01	Han Chinese
Zonisamide	SJS/TEN	?HLA-A*02:07	Japan

*HLA-B*15:21 is an important association with carbamazepine SJS/TEN.

TABLE XCIX. Valproic acid oral desensitization protocol*

Interval (d)	Solution†	Volume (mL)	Daily dose (mg)
1-2	A	0.5	0.05
3-4	A	1	0.1
5-6	A	2.5	0.25
7-8	A	5	0.5
9-10	A	7.5	0.75
11-12	B	0.2	1
13-14	B	0.5	2.5
15-16	B	1	5
17-18	B	2	10
19-20	B	5	25
21-22	C	0.25	50
23-24	C	0.5	100
25-26	1 tablet	—	200
27-28	1 tablet twice a day	—	400
29-30	2 tablets twice a day	—	800

*As adapted by Toker et al.[881]
†Solution A: The solution was made by 1:50 dilution of solution B to a final concentration of 0.1 mg/mL. Solution B: The solution was prepared by diluting 2 mL of valproic acid solution (Depalept Oral Solution-CTS; 200 mg/mL) into a volume of 78 mL diluent (water) to a final concentration of 5 mg/mL. Solution C: Valproic acid oral solution (Depalept Oral Solution-CTS; 200 mg/mL). Valproic acid tablet (Depalept-CTS; 200 mg).

renal impairment, or history of widespread cutaneous eruptions with fever (Table XCVII).[13] Although allopurinol desensitization is largely successful, there have been reports of unmanageable recurrent rash and significant adverse reactions necessitating discontinuation of treatment.[13,854] Therefore, continued vigilance and monitoring are essential.

Antiepileptics (by Sarah L. Garon, MD, and Elizabeth Phillips, MD)

General. Aromatic antiepileptic drugs such as carbamazepine, oxcarbazepine, phenytoin, phenobarbital, lamotrigine, felbamate, and zonisamide have been associated with a number of hypersensitivity drug reactions, and a clinical presentation of benign, delayed rash is the most common manifestation (rates ranging from 5% to 17%). On the spectrum of potentially severe immunologically mediated adverse drug reactions (IM-ADRs), isolated benign exanthem is most common and mild; however, more SCARs exist, which include DRESS, AGEP, fixed drug eruption, and SJS/TEN.[855] These SCAR syndromes differ according to their clinical presentation, morbidity and mortality, time between initiation of the drug and onset of symptoms, immunopathogenesis, HLA and pharmacogenomic associations, and utility of *in vivo* (patch and delayed prick/intradermal) testing (Table XCVIII).[353,856,857] SCARs are not rare in

TABLE C. Desensitization protocol for pentobarbital[877,880]

Desensitization strategy
• Pentobarbital 0.25 μg/kg × ____ kg = ____ μg in 5 mL normal saline (NS) intravenously (IV) × 1 over 30 min, followed immediately by
• Pentobarbital 2.5 μg/kg × ____kg = ____ μg in 5 mL NS IV × 1 over 30 min, followed immediately by
• Pentobarbital 25 μg/kg × ____kg = ____ μg in 5 mL NS IV × 1 over 30 min, followed immediately by
• Pentobarbital 250 μg/kg × ____kg = ____ μg in 5 mL NS IV × 1 over 30 min, followed immediately by
• Pentobarbital 500 μg/kg × ____kg = ____ μg in 5 mL NS IV × 1 over 30 min, followed immediately by
• Pentobarbital 10 mg/kg × ____kg = ____ μg in 5 mL NS IV × 1 over 120 min, followed immediately by the full therapeutic starting dose
Full therapeutic starting dose: *Must be continued on schedule without interruption*
• Pentobarbital 1 mg/kg/h × ____kg = ____ mg/h IV continuous solution

TABLE CI. Intravenous iron preparations*

Drug	Trade name	Available in the United States	Test dose	TDI*	FDA boxed warning
HMW-ID	DexFerrum; Imferon	N (discontinued)	Y	Y	Y
LMW-ID	InFeD	Y	Y	Y	Y
Ferric gluconate	Ferrlecit	Y	N	N	N
Iron sucrose	Venofer	Y	N	N	N
Ferumoxytol	Feraheme	Y	N	Y	Y
Iron isomaltoside	Monofer	Y	N	Y	N
Ferric carboxymaltose	Injectafer	Y	N	N	N

ID, Iron dextran; *LMW*, low molecular weight; *N*, no; *TDI*, total dose infusion; *Y*, yes.
*Allowing single dose administration of a patient's entire iron requirement, rather than needing multiple smaller doses.

TABLE CII. Treatment of parenteral iron reactions

Mild	Arthralgias, myalgias, flushing, mild chest tightness, mild hypotension, nausea, itching	Pause infusion until symptoms resolve, then resume at 25%-50% rate. Consider pausing and giving a steroid if recurs. Observe 60 min after completion of infusion
Mild with urticaria	As above, with urticaria	Pause infusion, give antihistamine or steroid. Observe until symptoms subside, then resume infusion
Moderate	Severe chest pain, cough, nausea, tachycardia, hypotension	Stop infusion. Give IV fluids, steroids, and antihistamines. Consider alternative agent
Severe	Bronchospasm, stridor, hypoxemia, significant hypotension, tachycardia, angioedema	Stop infusion. Give epinephrine, oxygen, inhaled β_2-agonists, IV fluids, steroids, antihistamines, other resuscitation
Delayed	Arthralgias, myalgias, flushing	Corticosteroid premedication NSAIDs for symptomatic treatment

IV, Intravenous.

anticonvulsant drug users. Immediate IgE-mediated reactions such as urticaria or angioedema are rarely described as compared with the DHR.

Major symptoms of hypersensitivity. The term "anticonvulsant hypersensitivity syndrome" has been used to encapsulate the triad of fever, rash, and internal organ involvement, but other features such as lymphadenopathy and eosinophilia are commonly present.[855] This is likely a form of DRESS when anticonvulsant therapy is implicated. In early literature, the clinical cross-reactivity between aromatic amines such as phenytoin, carbamazepine, and phenobarbital was as high as 75% as ascertained by positive rechallenge reactions.[855] In European populations, an estimate of the higher end of risk of this syndrome is 4.5/10,000. Later studies have shown that many severe IM-ADRs associated with aromatic antiepileptic drugs are associated with specific HLA alleles; however, even before these, case reports suggested a familial predisposition and 10- to 1000-fold overrepresentation of some of the IM-ADRs in specific ethnicities in which the risk HLA alleles are prevalent.[353,856-858]

Immediate-type, IgE-mediated symptoms have been described in the literature. Case reports have described urticaria and/or angioedema to oxcarbazapine in 9 pediatric patients, to phenobarbital in 1 pediatric patient, to carbamazepine in an adult, and tongue angioedema to phenytoin in a child.[859,860] Anaphylaxis is rarely reported. It is important to be aware that immediate-type symptoms may occur, but these are not as frequent as delayed-type drug hypersensitivity reactions. Many of these case reports cannot be validated as truly mediated by IgE. Also, angioedema or other benign exanthem may be misdiagnosed as IgE-mediated when in fact it may be the presenting cutaneous manifestation of anticonvulsant syndrome.

One study examining different appearances of rashes associated with anticonvulsants reported that aromatic anticonvulsants are significantly associated with IgE-mediated (immediate) type I and cell-mediated (nonimmediate or delayed) type IV drug

TABLE CIII. Sample 12-step rapid desensitization protocol for ferric gluconate

Solution (100 mL each)		Concentration (mg/mL)		mg/bag		Volume infused (mL)
1		0.0125		1.25		9.25
2		0.125		12.5		18.75
3		1.2254		122.5		100
Step	**Solution**	**Rate (mL/h)**	**Time (min)**	**Volume (mL)**	**Dose (mg)**	**Cumulative dose (mg)**
1	1	2	15	0.5	0.0063	0.0063
2	1	5	15	1.25	0.0156	0.0219
3	1	10	15	2.5	0.0313	0.0531
4	1	20	15	5	0.0625	0.1156
5	2	5	15	1.25	0.1563	0.2719
6	2	10	15	2.5	0.3125	0.5844
7	2	20	15	5	0.6250	1.2094
8	2	40	15	10	1.2500	2.4594
9	3	10	15	2.5	3.0635	5.5229
10	3	20	15	5	6.1270	11.6499
11	3	40	15	10	12.2541	23.9040
12	3	80	61.875	82.5	101.0960	125.0000

hypersensitivity reaction, with a reported odds ratio of 2.15 and 6.06, respectively. The caveat, however, was that clinical phenotypes were not validated by additional formal causality assessment or additional diagnostic (eg, skin) testing. The aromatic amine anticonvulsants have been more significantly associated with delayed cutaneous reactions.[861]

Pharmacogenetic studies. The aromatic amine anticonvulsants share an aromatic benzene ring and are metabolized by SMZ-TMP enzymes to hydroxylated aromatic amine compounds (arene oxides). It was initially hypothesized that reactive metabolites of these drugs haptenated cellular proteins leading to an antigen-specific response. More recently, cellular models have supported HLA-restricted, dose-dependent, and noncovalent interactions between these aromatic amine anticonvulsant drugs and HLA molecules/T-cell receptor. The genetic associations have been strongest for HLA serotype B75 alleles, such as HLA-B*15:02 and carbamazepine SJS/TEN, which are more prevalent in Southeast Asian populations. Since 2007, the FDA has recommended HLA-B*15:02 screening for all patients of known or suspected Southeast Asian ancestry before initiating carbamazepine treatment. A prospective 1-arm study from Taiwan has supported a reduction in the incidence of carbamazepine SJS/TEN in association with HLA-B*15:02 screening.[862,863] Another study from Hong Kong showed that mandated HLA-B*15:02 screening did not result in a reduction in the incidence of SJS/TEN overall. This is because HLA-B*15:02 testing appeared to lead to displacement of carbamazepine prescribing with the prescription of phenytoin and a subsequent increase in phenytoin SJS/TEN, thus underscoring the fact that provider engagement and education is often necessary for clinical translation.[864] HLA risk alleles have had a low (<5%) positive predictive value for the development of IM-ADRs associated with antiepileptic drugs, suggesting that other factors are important in the immunopathogenesis. More recently, a dominant T-cell receptor clonotype has been found from blister fluid and PBMCs in patients with acute- and recovery-phase carbamazepine SJS/TEN.[353]

Testing and diagnosis. The utility and cost-effectiveness of HLA screening is currently largely based on the population prevalence of disease carriage rate of the specific HLA allele in the population in question and the positive predictive value of the HLA risk allele for the development of the IM-ADR. The number needed to treat to prevent 1 case of IM-ADR can vary from a few hundred to more than 10,000.[353,857] Cost-effectiveness decisions, however, are also driven by the fact that SJS/TEN, the most severe of IM-ADRs associated with these aromatic anticonvulsants, has significant long-term morbidity and mortality of up to 50% or higher, particularly in aging populations.[865-867] The prevalence of HLA-B*15:02 is 7% to 15% or higher in Southeast Asia and India but less than 1% in populations of European and African ancestry.[353] HLA-A*31:01 has been associated with carbamazepine exanthem (maculopapular eruption) and DRESS in multiple ethnicities including European. However, the generalizability of an association between HLA-A*31:01 and carbamazepine SJS/TEN needs to be further clarified.[353,858,865,867,868] Lamotrigine has also been associated with a risk of severe immunologically mediated drug reactions, though it is primarily glucuronidated rather than oxidized like the other aromatic anticonvulsants.[855] Graded dose introduction has been an effective way to reduce the incidence of isolated drug eruptions associated with lamotrigine. Valproic acid and newer structurally disparate anticonvulsants have been safe to administer in patients with reactions to the aromatic antiepileptic drugs. However, the risk of a cutaneous reaction is increased with concurrent use of valproic acid and lamotrigine because of metabolic interactions that lead to an increased elimination half-life of lamotrigine and accumulation of the parent drug.[869]

In vivo testing such as patch testing has been used successfully in such studies, showing sensitivity of more than 80%, particularly in carbamazepine-associated DRESS in some studies, but significantly less than 50% in others. Overall sensitivity for patch testing with antiepileptic drugs varies from less than 20% to more than 80%.[52,870,871] Patch tests should be left *in situ* for 48 hours and ideally read at 48 hours, 72 hours, 96 hours, and 1 week. The vehicle and concentration appear to be important, and

sensitivity is highest in DRESS>AGEP>SJS/TEN.[52] For patch testing, it is recommended to use between 1% and 10% (wt/wt) of pure drug or 30% (wt/wt) concentration of the powdered commercial tablet when the pure drug form cannot be patch tested. Variability in positive results of patch testing with varying concentrations across different anticonvulsants signifies the need for patch testing with several concentrations for accurate results, most commonly 1%, 10%, and 30% of the various antiepileptics in petrolatum.[52,871,872] Carbamazepine patch testing appears to be associated with the highest sensitivity, and some studies have been able to show a significant cross-reactivity on patch testing between drugs such as carbamazepine and phenytoin.[52,871,872] The genetic significance of this is still not known because there is a much weaker association between phenytoin SJS/TEN and HLA-B*15:02. From a recent genome-wide association study that included populations from Taiwan, Malaysia, and Japan with phenytoin SJS/TEN/DRESS, a strong association was identified with a poor metabolizing genotype of the primary oxidizing enzyme of phenytoin, CYP2C9 (CYP2C9*3), and not significantly with genes in the HLA region.[873-875] One study showed greater sensitivity of delayed prick and intradermal testing compared with patch testing, but this has not been universally applied.[52] The lack of commercial availability of sterile intravenous solutions for the aromatic anticonvulsants has limited the use of intradermal testing for anticonvulsant hypersensitivity.[52] In addition, prick and intradermal testing have been avoided in very severe reactions such as SJS/TEN because of the rare instances of systemic reactions. *Ex vivo* and *in vitro* tests such as ELISpot, lymphocyte toxicity assay, and lymphocyte transformation tests for the aromatic anticonvulsant drugs have been used in the research setting. They currently lack sufficient positive and negative predictive value and have not been quality assured for clinical use.[353,855,857,876]

True immediate reactions (IgE-mediated) to antiepileptic drugs including the aromatic amine anticonvulsants are very uncommon, and validated skin testing protocols for immediate hypersensitivity reactions to antiepileptics are hence not available. One case study has described successful skin testing to phenobarbital and pentobarbital. For skin testing, 0.1 mg/mL and 1 mg/mL concentrations were nonirritating in both the patient and control and may be considered.[877] Caution is also advised, because on second exposure to the implicated anticonvulsant drug or a structurally related aromatic amine anticonvulsant, a reaction that is actually T-cell—mediated can appear immediate or accelerated in nature because it is a second-exposure memory T-cell response. These reactions are mechanistically distinct from IgE-mediated reactions and non—IgE-mediated mast cell activation. Many are potentially severe reactions that can be life-threatening with continued dosing of the drugs.

Management. Many patients with hypersensitivity to one aromatic anticonvulsant may experience similar symptoms with other cross-reactive aromatic anticonvulsants, but there are alternative agents without this structural similarity. Desensitization and slow reintroduction protocols exist and are aimed toward patients with histories of delayed reactions including mild rashes without accompanying fever, internal organ, mucosal, or severe skin involvement.[878,879] SCAR hypersensitivity reactions should result in discontinuation of the offending drug, and desensitization protocols should not be performed on these patients. There are a few published desensitization protocols in the literature to both oxcarbazepine and valproic acid following mild-delayed rashes (Table XCIX).[877,878,880,881] Both an oral desensitization to phenobarbital and an intravenous desensitization to pentobarbital have been reported to be successful in cases of immediate hypersensitivity (Table C).[877,880]

Benzodiazepines (by Parul Kothari, MD)

General. Benzodiazepines are prescribed for a wide variety of disorders, including anxiety, seizures, insomnia, muscle spasms, and alcohol withdrawal. They act in the central nervous system to enhance the inhibitory effect of γ-aminobutyric acid. Because they have the potential to be abused, they are controlled substances regulated by the US Drug Enforcement Agency. They are commonly classified as short-, intermediate-, or long-acting, on the basis of their half-life.

Structurally, benzodiazepines are composed of benzene and diazepine rings that are fused together. Benzodiazepines differ by their side chains, which can alter their specific pharmacologic properties. Among the structural differences, alprazolam has a unique triazole ring and tetrazepam a cyclohexene ring.

Major symptoms of hypersensitivity. Allergic reactions to benzodiazepines are rare, and most of the literature is limited to case reports and small case series.[882-887] Both immediate and delayed reactions have been reported to range in severity from mild to severe, including SJS and TEN. A recent cohort study estimated the cumulative incidence of SJS/TEN to benzodiazepines to be 3.76 per million new users.[886] The most common benzodiazepine implicated in the literature to date has been tetrazepam, which is not available in the United States.

Diagnosis. Although diagnostic testing for hypersensitivity reactions to benzodiazepines is not validated, there are reports in the literature of skin and patch testing to support the diagnosis. Currently, the determination of a benzodiazepine allergy relies on a careful history with attention to objective findings at the time of the reaction. For midazolam, the maximum nonirritating concentration for skin testing has been reported as 1 to 5 mg/mL and 0.25 to 0.5 mg/mL for PTs and IDTs, respectively.[79,888]

Management. Given the rarity of allergic reactions to benzodiazepines, there are no studies that have evaluated cross-reactivity among members of this class of medication. In a case report of an IgE-mediated hypersensitivity reaction to tetrazepam, the patient had a negative skin test result and tolerated a challenge to diazepam.[885] In a case series of delayed cutaneous reactions to tetrazepam, all 9 subjects were tolerant to other benzodiazepines, as demonstrated by negative testing result and/or challenge.[883] This was attributed to differences between the structure of tetrazepam and other benzodiazepines. However, others have reported cross-reactivity between tetrazepam and diazepam as well as contact dermatitis to multiple benzodiazepines.[884,889] If an alternative benzodiazepine is required, one that has been previously tolerated should be used and/or a supervised oral challenge performed. Currently, there are no desensitization protocols for benzodiazepines in the literature.

Muscarinic antagonists (by Samantha Minnicozzi, MD)

General. Muscarinic antagonists are drugs that bind to muscarinic receptors and inhibit acetylcholine from binding and its subsequent downstream effects. For example, atropine is used

for the treatment of childhood myopia and for pupillary dilation and bradycardia, and as an antidote for cholinergic toxicity. Scopolamine is used to prevent nausea during chemotherapy regimens and postoperatively. Glycopyrrolate decreases secretions, and is commonly used preoperatively and perioperatively for airway management. Oxybutynin is used to treat patients with bladder difficulties including urge and incontinence.

All antimuscarinic agents have wide side-effect profiles depending on which muscarinic receptor is targeted. Common side effects of antimuscarinic agents include mydriasis, dry mouth, tachycardia, agitation, delirium, and hyperthermia. Infants and children are particularly susceptible to these hyperthermic effects.

A review of topical atropine use found a 1% to 4% risk of minor reactions, with more severe effects observed with intravenous administration including cardiac arrhythmias.[890,891] Hypersensitivity reactions have rarely been reported, with very few case reports describing atropine and cyclopentolate causing suspected IgE-mediated reactions.[892-894]

Major symptoms of hypersensitivity. Among the antimuscarinic drugs, atropine has the largest accumulation of case reports describing anaphylaxis to parenteral and topical formulations. In a review of atropine applied topically in pediatric patients for the treatment of myopia, 3.2% developed allergic conjunctivitis, with 0.8% experiencing an allergic dermatitis.[890] In case reports of suspected atropine and cyclopentolate, anaphylaxis symptoms included generalized urticaria, facial and eyelid edema, pruritus, vomiting, and hypotension.[892-895]

Delayed hypersensitivities and contact allergies to antimuscarinic agents are another drug-related allergy. In a large study evaluating the safety of topical atropine for the treatment of myopia in children, up to 0.8% developed a contact allergy.[890] Oral oxybutynin has been implicated in a case of fixed drug eruption that continued intermittently over months, coinciding with the use of oxybutynin, and resolved only once therapy was discontinued.[896]

Inhaled antimuscarinic agents are a mainstay in the treatment of COPD. A review of the literature on either asthma or COPD found no case reports of history of inhaled agents such as ipratropium or tiotropium causing immediate hypersensitivity reactions. There was a single case report of a patient with COPD who developed an intermittent whole-body pruritic rash for several years.[897] A biopsy of the rash was consistent with a drug eruption. The patient was initially given a tiotropium inhaler, which was discontinued. Following discontinuation, the patient was started on an ipratropium metered-dose inhaler, after which the rash recurred 3 days later and disappeared 5 days after discontinuing therapy. The patient continued to develop a similar rash waxing and waning with the use of umeclidinium and aclidinium until all inhaled antimuscarinic therapy was discontinued.[897]

Diagnosis. Skin testing for the evaluation of immediate hypersensitivity to antimuscarinic agents has not been commonly performed and has not been validated on review of the literature. Cavanah and Casale[898] describe antimuscarinic intradermal skin testing to atropine and scopolamine in 7 healthy volunteers using volumes of 20 nmol and 2 nmol. The solutions used for testing in this protocol were created by diluting either atropine or scopolamine in 0.9% saline, 0.03% human albumin, and 0.4% phenol in water and then buffering the solution to a pH of 6.5 to 7.5. All subjects developed a wheal-and-flare reaction to atropine at both doses.[898] In comparison, all subjects reacted with a wheal-and-flare response to 20 nmol of scopolamine and none had a response to 2 nmol.[898]

Fisher and Bowey[899] performed atropine skin testing as part of their perioperative anaphylaxis evaluation in 10 individuals. They performed skin prick testing using undiluted atropine at a concentration of 0.6 mg/mL and intradermal testing at a dilution of 1:1000.[899] Similarly, Cabrera-Freitag et al[892] performed skin prick and intradermal drug testing to atropine to evaluate a case of anaphylaxis. Atropine was used at a concentration of 1 mg/mL for skin prick testing and a dilution of 0.1 mg/mL for intradermal testing. The patient had a positive result on intradermal testing, with negative intradermal testing result in 10 control subjects.[892]

Management. There is little evidence in the literature regarding cross-reactivity in patients with reported allergy to one antimuscarinic agent and their ability to tolerate other antimuscarinic agents. The case reports discussing allergic reactions recommend avoidance of similar antimuscarinic drugs in the future and do not discuss class alternatives. Desensitization protocols to antimuscarinic agents are yet to be described.

Iron (by Anne Liu, MD)

General. Intravenous iron is an essential aspect of iron-deficiency anemia when side effects or absorption limit the use of oral formulations. Intravenous iron preparations are colloids of iron-carbohydrate nanoparticles that vary by iron core size and type of surrounding carbohydrate, processed and released as free labile iron.

Formulations available in the United States include low-molecular-weight iron dextran, ferric gluconate, iron sucrose, ferumoxytol, iron isomaltoside, and ferric carboxymaltose (Table CI). High-molecular-weight (HMW) iron dextrans were discontinued in the United States.

Hypersensitivity reactions. Labile plasma iron may produce nonspecific oxidative stress and complement activation.[900,901] Excluding HMW iron dextrans, evidence for immune complex formation and IgE-mediated mechanisms is paltry, and tryptase elevation is exceedingly rare.[902,903]

Adverse reactions may be infusion rate—dependent and typically manifest as dyspnea, chest and/or back pain, acute arthralgias and myalgias, hypotension, tachycardia, nausea/vomiting, and pruritus.[904-906] Minor reactions usually abate without treatment or with rate reduction and may not recur on rechallenge.[905] Angioedema and urticaria may signal a distinct reaction type. Severe reactions including anaphylaxis can be fatal. Rarely, delayed reactions may exhibit hypotension, arthralgias/myalgias, malaise, and vomiting. Iron sucrose can uniquely cause peripheral edema and renal injury in a rate- and concentration-related manner.[906,907]

Excluding HMW iron dextrans, incidence of serious adverse reactions is less than 1 in 200,000, accounting for approximately 0 to 5 deaths per year in the United States.[906,908] The high reaction rate and mortality associated with iron dextrans has been attributed to the HMW iron dextran formulation.[908-910] Limited data suggest iron isomaltoside carries a higher reaction risk than ferric carboxymaltose.[911] Significant differences in reaction risk

have not been shown among low-molecular-weight iron dextran, iron sucrose, ferric gluconate, and ferric carboxymaltose.[908,912-917]

Adverse event reporting initially suggested an increased risk of fatal reactions from ferumoxytol, but randomized comparisons of ferumoxytol with iron sucrose and ferric carboxymaltose reported similar rates of adverse reactions.[918-921]

Risk factors for severe hypersensitivity reactions include atopy and multiple drug allergies including previous iron hypersensitivity reactions.[900,905,922]

Diagnosis. Evaluation of an iron reaction should document the specific product and dose, route, and rate of administration, and include a detailed description of the reaction, treatment, and response.

Graded challenge is required only for low-molecular-weight iron dextrans and may not predict serious hypersensitivity reactions.[922] Skin testing has limited utility because most reactions are not IgE-mediated, but it may detect a subset of patients who are sensitized via typical allergic pathways. A protocol for ferric gluconate skin testing has been used: skin prick at 12.5 mg/mL, and IDT at 0.0125, 0.125, and 1.25 mg/mL at the Brigham and Women's Hospital. Skin testing to iron sucrose should not be performed, because a permanent tattoo can form from deposition of iron pigment.

Management. Table CII outlines suggested reaction treatments based on expert panel consensus.[916,922] Premedication with antihistamines is not advised because of ineffectiveness and side effects.[916,922] Switching agents can be considered in patients with mild to moderate reactions, but expert panels advise avoiding all parenteral iron after a severe reaction.[916] Ferric gluconate and iron sucrose, but not ferumoxytol, are considered alternatives for patients sensitive to iron dextran.[902,923,924]

Desensitization to HMW iron dextrans has been reported.[925,926] Desensitization protocols to ferric carboxymaltose and iron sucrose have been reported in patients with a history of anaphylaxis to other iron products.[927,928] In the Brigham and Women's Hospital experience, allergists have successfully performed ferric gluconate desensitizations (Table CIII). Desensitization to iron dextrans has been difficult to complete because of treatment-refractory reactions. Iron sucrose desensitization is not done because of poor stability at lower concentrations. Further data are needed to elucidate a role for rapid desensitization after parenteral iron anaphylaxis.

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