

Prevention of Drug Hypersensitivity Reactions: Prescreening and Premedication



Bernard Yu-Hor Thong, MBBS, MRCP (UK), FRCP (Edin)^a, Alessandra Vultaggio, MD, PhD^b, Ticha Rerkpattanapipat, MD^c, and Rik Schrijvers, MD, PhD^d *Singapore; Leuven, Belgium; Bangkok, Thailand; and Florence, Italy*

INFORMATION FOR CATEGORY 1 CME CREDIT

Credit can now be obtained, free for a limited time, by reading the review articles in this issue. Please note the following instructions.

Method of Physician Participation in Learning Process: The core material for these activities can be read in this issue of the Journal or online at the *JACI: In Practice* Web site: www.jaci-inpractice.org/. The accompanying tests may only be submitted online at www.jaci-inpractice.org/. Fax or other copies will not be accepted.

Date of Original Release: August 1, 2021. Credit may be obtained for these courses until July 31, 2022.

Copyright Statement: Copyright © 2021-2023. All rights reserved.

Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for

physicians. The AAAAI designates this journal-based CME activity for 1.00 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: Bernard Yu-Hor Thong, MBBS, MRCP (UK), FRCP (Edin), Rik Schrijvers, MD, PhD, Ticha Rerkpattanapipat, MD, and Alessandra Vultaggio, MD, PhD (authors); David A. Khan, MD (editor)

Learning objectives:

1. To clinically correlate the immunological mechanisms with various phenotypes and endotypes of drug hypersensitivity reactions.
2. To understand the benefits and limitation of premedications in the prevention of specific types of drug hypersensitivity reactions.
3. To use appropriate *in vivo*, *in vitro*, and pharmacogenomic tests in the prevention of serious systemic drug hypersensitivity reactions.

Recognition of Commercial Support: This CME has not received external commercial support.

Disclosure of Relevant Financial Relationships with Commercial Interests: The authors declare that they have no relevant conflicts of interest. D. A. Khan declares no relevant conflicts of interest.

Drug hypersensitivity reactions (DHR) are heterogeneous in their pathomechanisms, clinical presentation, severity, and outcomes. Novel DHR mechanisms, phenotypes, and endotypes have been described. The key to prevention from further exposure to the culprit drugs involves correct identification of the putative drug through a combination of *in vitro* and/or *in vivo* tests, accurate drug allergy labeling and reporting, and electronic decision support systems within electronic medical records to prevent future accidental prescribing. Prescreening and premedication, the focus of this review, may be a useful adjunct to preventive measures in certain situations. After an index immediate drug hypersensitivity reaction, prescreening may be useful in perioperative anaphylaxis, and iodinated (ICM)

and gadolinium-based contrast media (GCM) where the culprit and potential alternative agents are skin tested. In certain nonimmediate DHR, pharmacogenomic prescreening may be used before prescribing high-risk drugs (eg, carbamazepine and allopurinol) where specific human-leukocyte antigen genotypes are associated with severe cutaneous adverse reactions. Premedication with antihistamine and systemic corticosteroids is another therapeutic strategy to prevent infusion reactions for certain biologicals and chemotherapeutic agents, in cases of perioperative anaphylaxis, ICM and GCM DHR, and clonal mast cell disorders. Rapid drug desensitization may also be used to induce temporary tolerance in situations where there are limited alternative drugs. © 2021 American Academy of

^aDepartment of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, Singapore

^bImmunology Unit, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy

^cAllergy, Immunology and Rheumatology Division, Department of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

^dDepartment of Microbiology, Immunology and Transplantation, Allergy and Clinical Immunology Research Group, KU Leuven, Leuven, Belgium

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication February 20, 2021; revised April 3, 2021; accepted for publication April 7, 2021.

Corresponding author: Bernard Yu-Hor Thong, MBBS, MRCP (UK), FRCP (Edin), Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308344. E-mail: bernard_thong@ttsh.com.sg.

2213-2198

© 2021 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2021.04.006>

Abbreviations used

ADA- Antidrug antibody
BA- Biological agent
BTR- Breakthrough reaction
CRS- Cytokine release syndrome
DHR- Drug hypersensitivity reaction
EAACI- European Academy of Allergy Asthma and Clinical Immunology
GCM- Gadolinium-based contrast media
H1- Histamine-1
HLA- Human-leukocyte antigen
HSR- Hypersensitivity reaction
ICM- Iodinated contrast media
iDHR- Immediate drug hypersensitivity reaction
NERD- NSAID exacerbated respiratory disease
niDHR- Nonimmediate drug hypersensitivity reaction
NMBA- Neuromuscular blocking agent
NSAID- Nonsteroidal anti-inflammatory drug
RCM- Radiocontrast media
RDD- Rapid drug desensitization
SCAR- Severe cutaneous adverse reaction
sIgE- Specific IgE
TNF- Tumor necrosis factor

Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;9:2958-66)

Key words: Anaphylaxis; Desensitization; Pharmacogenomic testing; Stevens Johnson syndrome; Toxic epidermal necrolysis

Drug hypersensitivity reactions (DHR) are heterogeneous in their pathomechanisms, clinical presentation, severity, and outcomes.^{1,2} Severe cutaneous adverse reactions (SCAR), for example, Stevens Johnson syndrome/toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms, are potentially life-threatening nonimmediate drug hypersensitivity reactions (niDHR) associated with a high risk of morbidity and mortality.^{3,4} Anaphylaxis to a variety of drugs⁵ including beta-lactam antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), perioperative anesthetic agents, chemotherapeutic agents, and biologics are increasingly recognized to be mediated by a variety of mechanisms not limited to IgE.⁶ Prevention from further exposure involves correct identification of the putative drug through *in vitro* and/or *in vivo* tests,⁷ accurate allergy labeling and reporting, and electronic decision support systems within electronic medical records⁸ to prevent future accidental prescribing. In this review, we focus on the roles of prescreening and premedication in the treatment and prevention of future DHR.

NOVEL MECHANISMS OF DRUG HYPERSENSITIVITY REACTIONS

Gell and Coombs' classification categorizes hypersensitivity reactions (HSRs) into 4 subtypes (types I-IV) according to the type of immune response and the effector mechanism responsible for cell and tissue injury.⁹

This classification has some limitations in clinical practice as HSRs to novel drugs such as chemotherapeutic and biological agents (BAs) may involve other mechanisms.⁶ Apart from modulating the immune system, these are potentially immunogenic drugs leading to the formation of specific antidrug

antibodies (ADA) that may cause HSRs. For example, IgE-mediated allergy may occur in a “nonclassical” manner at the first administration of cetuximab,¹⁰ rituximab,¹¹ and taxanes.¹² This is because patients may have pre-existing antibodies specific to the drug, due to sensitization through tick bites (in the case of cetuximab) or through shared epitopes (in the case of rituximab and taxanes). The mechanism underlying cetuximab-induced anaphylaxis has modified our concepts about IgE antibodies against carbohydrates, not considered pathogenic previously.

Patients reactive to some monoclonal antibodies or other chemotherapeutic drugs have positive skin tests to the specific drug or detectable serum drug-specific IgE.^{13,14} However, BAs such as infliximab, natalizumab, and adalimumab are also able to induce the development of IgG ADA that directly activate basophils and neutrophils (via FcγRIII) and indirectly (via release of anaphylotoxins) through mast cells.^{15,16} IgG-mediated reactions, that occur after at least 1 drug administration, may be clinically indistinguishable from IgE-mediated events. The distinction between IgE and IgG-mediated reactions is that skin prick tests are negative for IgG-mediated reactions. BAs and chemotherapeutics may induce HSRs in an antibody-independent mechanism, such as cytokine release syndrome (CRS) and complement activation (for aggregates or additives such as lipid excipients). These types of reactions usually occur at the first/second drug administration, are usually self-limiting, but could clinically overlap with IgE and IgG-mediated reactions. Thus, novel drugs may induce HSRs through novel mechanisms, increasing the need for precision in the diagnosis and prevention of DHR.¹⁷ Of note, Pichler¹⁸ had already proposed, in 2006, a novel and specific classification for adverse drug reactions to BAs including 5 types of adverse side effects: alpha (CRS), beta (hypersensitivity), gamma (immune or cytokine imbalance syndromes), delta (cross-reactivity), and epsilon (non-immunological side effects).

More recently, a classification of immediate HSRs based on phenotypes, endotypes, and biomarkers has been proposed, applying a precision medicine-like approach to drug allergy.¹⁹ Phenotype may be defined as the set of observable characteristics, including the timing of onset, the symptom spectrum and severity, and the exposure pattern. Endotype refers to the effector cells and molecules involved in the HSR. The same phenotype of reactions can be sustained by different endotypes. In addition, a drug may induce HSRs via different mechanisms that in some patients may coexist (overlapping endotypes). Biomarkers, represented by objectively measurable *in vivo* and *in vitro* parameters, include skin testing (prick and intradermal test, patch test), serum drug-specific IgE, basophil activation test with the evaluation of surface markers of basophils activation (CD63 and CD203), tryptase, and in some cases cytokines (IL-6, tumor necrosis factor [TNF]). The evaluation of biomarkers useful for the identification of underlying mechanisms is key in assessing the feasibility of the drug provocation test and of desensitization to prevent further reactions in patients without any alternative therapy.

PREScreening

Perioperative anaphylaxis

In patients without a relevant history of a previous reaction, European Academy of Allergy Asthma and Clinical Immunology (EAACI) guidelines do not recommend routine preoperative testing for sensitization to any drug(s) or product(s) used in anesthesia.^{20,21} A thorough history taking for perioperative

reactions remains key to diagnosis. The incidence of perioperative anaphylaxis is reported to be around 1:10,000²² to 1:20,000.²⁰ Prospective studies suggest a higher incidence of 1:1480²³ to 1:3180,²⁴ and Savic et al even indicated that 1:353 procedures could meet the criteria of a potential perioperative anaphylaxis, suggesting a potential underreporting or referral bias.^{25,26} This low incidence does not justify preoperative allergy evaluation in all patients.

The predictive values of allergy tests, in particular *in vitro* tests in the general population, are unknown, and false-positive or false-negative results could negatively influence anesthesia, the procedure, or its timing. The sensitivity for IgE-mediated reactions varies. Specific IgE (sIgE) determination is only available for a limited number of perioperatively used drugs (succinylcholine, rocuronium, atracurium, chlorhexidine, latex, ethylene oxide, morphine, and cefazolin in the research context)²⁷ and are inadequate to predict non-IgE-mediated reactions. Moreover, studies indicate that sensitization to ammonium epitopes, as a marker for sensitization to neuromuscular blocking agents (NMBAs), can be as high as 5% to 10% in the general population²¹ and argues against screening in the general population.²⁸ In addition, patients with positive sIgE but negative skin tests for certain NMBAs have been reported to successfully receive this specific NMBA.²⁹ sIgE values for cefazolin, currently only available in a research context, were demonstrated to be similar in cefazolin-allergic patients compared with exposed controls, although a ratio of specific over total IgE of 1.42×10^{-3} had an improved sensitivity and specificity (of 49% and 94%, respectively).²⁷ Sensitivity and specificity of chlorhexidine sIgE were 94.7% and 90.1%, respectively, for a receiver operating characteristic analysis optimized threshold of 0.20 kUA/L,³⁰ indicating that substantial false-negative and -positive results might arise from routine screening. Thus, the determination of sIgE should not be applied in isolation and performed as a pre-emptive screening tool in the general population. It should only be embedded in an allergy workup in patients with a prior reaction.²⁸ These sIgE tests are not widely available in the United States.

Prescreening for perioperative anaphylaxis includes a preoperative questionnaire that aims to identify relevant pre-existing allergies (including latex).²⁰ In addition, a history of an unexplained perioperative anaphylaxis is considered an important risk factor for a future event and should always prompt an allergy workup.³¹ A baseline serum tryptase should be drawn after any episode of perioperative anaphylaxis. Secondary prevention using skin testing with all perioperative agents (including disinfectants and relevant excipients) given before the reaction, with or without additional *in vitro* tests (sIgE determination and/or basophil activation testing) and drug provocation tests where appropriate, is recommended by allergy practice guidelines.^{20,32-35} Such a workup aims to identify potential culprit(s) and cross-reactive molecule(s), and provide safe alternatives using an evaluation of all potential causes. The negative predictive value of an allergy workup for perioperative anaphylaxis is high and estimated to be around 96%,^{29,36-38} although large series are awaited. Cases of repeat anaphylaxis were demonstrated to be due to incomplete referral information,³⁸ underlying clonal mast cell disorder,^{37,38} or accidental re-exposure as shown for chlorhexidine in up to one-third of allergic patients.³⁹ Routine screening for underlying clonal mast cell disorders, associated with a higher risk for severe perioperative reactions to either specific and/or nonspecific triggers,^{32,40} is not recommended. However, cases experiencing NMBA-induced

anaphylaxis despite negative skin testing for NMBAs have been reported,^{36,41} indicating the need for continued vigilance, including consideration of IgE-independent anaphylactic reactions mediated through activation of the mast cell receptor Mas-related G-protein coupled receptor member X². False-negative skin tests at first evaluation or re-sensitization have been put forward as an explanation. Whether additional drug provocation testing for NMBA, the current gold standard in a drug allergy workup, would also apply to patients with negative skin testing for NMBA remains to be determined.⁴² Drug provocation testing for NMBAs is carried out in a few highly specialized centers, up to 1:10 of the therapeutic dose. This is limited by the sensitivity of the drug provocation test at this dose and risk of requiring mechanical ventilation at higher doses. Thus, most centers would for practical purposes defer the use of the skin test negative NMBA until the next surgery requiring anesthesia.

Iodinated and gadolinium-based contrast media

Radiocontrast media (RCM) may lead to iDHR and niDHR, with iDHR being further classified into non-IgE- and IgE-mediated reactions.⁴³⁻⁴⁵ The latter constitutes a minority of iDHR, especially those with a severe clinical presentation.⁴⁶⁻⁴⁹

Routine prescreening using intradermal skin testing for RCM hypersensitivity without any history of DHR was not found to be useful.⁵⁰ Currently, primary prevention via screening for potential iDHR and niDHR after iodinated contrast media (ICM) or gadolinium-based contrast media (GCM) using *in vitro* or *in vivo* tests is neither advised nor possible. In patients who have experienced a DHR after ICM, skin testing has been demonstrated to have a high negative predictive value, around 93%, mostly for iDHR and less for niDHR.^{47,49,51-53} Prescreening for RCM DHR includes a questionnaire.

PREPRESCRIPTION PHARMACOGENOMIC SCREENING

Long before the classification of DHR phenotypes-endotypes-biomarkers,^{6,54} many pharmacogenomic studies had revealed strong associations between SCAR and genes encoding human-leukocyte antigens (HLAs) in drug- and ethnicity-specific patterns.⁵⁵ HLA-B*57:01 genotype testing before new prescriptions of abacavir, HLA-B*15:02 before carbamazepine, and HLA-B*58:01 before allopurinol prescriptions^{56,57} have become standard of care in some countries in Asia. The cost-effectiveness of pretesting is dependent on various factors including HLA-gene frequencies, geographical and ethnic differences, cost of the genotype test, country-specific health care financing and subsidy models, and availability of low-cost alternative drugs.⁵⁸

NSAID HSRs have been classified into various phenotypes including NSAID-exacerbated respiratory disease (NERD), NSAID-exacerbated cutaneous disease, and NSAID-induced urticaria angioedema.⁵⁹ More than 100 genetic variants have been identified in association with NERD, the majority mediated by single nucleotide polymorphisms of genes that regulate mRNA and protein expression responsible for prostaglandin and leukotriene metabolism, for example, *LTC4S*, *ALOX5*, *CYSLTR1*, *CYSLTR2*, *TBX*, *EP2*, and *COX2*. Epigenetic mechanisms, for example, dysregulation of CpG methylation, have been shown to play a role in NERD pathogenesis. However, a wide variety of different biomarkers in serum, urine, sputum, and nasal polyps have been shown to be associated with

NERD alone, making endotype-genotype correlations challenging.^{59,60} Prescreening is currently impossible.

Immediate reactions to beta-lactam antibiotics have to date been found to be associated mainly with the IgE pathways (IL13, IL4R, LGALS3, and NOD2) and antigen presentation (HLA-DRA),⁶¹ although HLA-DRB1*10:01 has also been found to be a risk factor for iDHR to penicillins.⁶² Thus, much more remains to be known before pharmacogenomics, and endotyping can be used to correlate with different phenotypes of a variety of DHR. Current studies have not supported avoiding beta-lactams in individuals with a family history of beta-lactam allergy. The evidence for prescreening is summarized in Table I.

PREMEDICATION

The Joint Task Force on Anaphylaxis Practice Parameters 2020 using the GRADE methodology conditionally recommends that:³⁵

- Evidence supports a role for antihistamine and/or glucocorticoid premedication in specific chemotherapy protocols.
- Evidence is lacking to support the routine use of antihistamines and/or glucocorticoid premedication in patients receiving low- or iso-osmolar contrast material to prevent recurrent RCM anaphylaxis.

Premedication for infusion reactions for biologicals and chemotherapeutic agents

Premedication with antihistamines, acetaminophen, and corticosteroids is a common practice to prevent infusion reactions in the majority of monoclonal antibodies, especially if intravenously administered, with no impact on the efficacy of the drug itself. Premedication is also included in some desensitization protocols. Dexamethasone is the most frequently used corticosteroid in the prevention of chemotherapeutic agent–induced HSRs, due to its potency, long duration of action, and antiemetic function, together with diphenhydramine, the most commonly employed histamine-1 (H1) receptor antagonist for the prevention of HSRs. Cetirizine appears to be a viable substitute for diphenhydramine for the prevention of infusion reactions with cetuximab, paclitaxel, and rituximab infusions in adults, although confirmatory prospective studies are needed.⁶³

The combination of corticosteroid and antihistamine seems to induce fewer reactions overall and fewer severe infusion reactions, at least for some products such as cetuximab.⁶⁴ However, the optimal prophylaxis and its efficacy depends on the nature of the event and its underlying mechanisms. Premedication with corticosteroids and antihistamines at commonly used doses is not sufficient to prevent the ADA-mediated HSRs, especially if ADA belongs to the IgE isotype, for example, first-dose cetuximab-related reactions. High dose of intravenous corticosteroid did not consistently prevent HSRs in patients with antibodies to infliximab.⁶⁴⁻⁶⁷

Premedication may prevent or dampen inflammatory reactions, such as CRS induced by monoclonal antibodies used in cancer therapy.⁶⁸ A protective role of anti-TNF alpha agents toward CRS induced by rituximab and muromonab has been reported in small oncology case series.^{69,70} The value of premedication may decrease after the first or second infusion for those drugs that are more frequently complicated by infusion reactions at the first or second dose. Discontinuation of premedication in paclitaxel-treated patients with breast cancer who have not experienced an HSR with the first 2 doses of the

TABLE I. Prescreening

Prevention of drug hypersensitivity reactions
• Primary prevention: no role • Secondary prevention: in individuals with a previous hypersensitivity reaction
Perioperative anaphylaxis
• Evidence supports a role for ○ preoperative questionnaire: to identify relevant pre-existing allergies (including latex) ○ baseline serum tryptase ○ skin prick and intradermal testing with all perioperative agents (neuromuscular blocking agents [NMBAs], opioids, local/regional anesthetic agents, hypnotics, benzodiazepines, antibiotics, disinfectants, relevant excipients) ○ certain <i>in vitro</i> tests (specific IgE determination and/or basophil activation testing) • Evidence is lacking to support ○ drug provocation tests (up to 1:10 of therapeutic dose of NMBAs; associated with risks of hypersensitivity reaction and need for mechanical ventilation; for practical purposes, consider deferring the use of the skin test negative perioperative drugs until the next surgery requiring anesthesia)
Iodinated and gadolinium-based contrast media
• Evidence supports a role for ○ preprocedure questionnaire: to identify exposure and clinical reactions to previous contrast media ○ skin prick and intradermal testing (for the index and alternative agents: high negative predictive value, around 93% for immediate hypersensitivity reactions, less for nonimmediate reactions) ○ drug provocation tests (for skin test negative contrast media) • Evidence is lacking to support ○ <i>in vitro</i> tests (not commercially available)
Pharmacogenomic screening for drugs with high risk of severe cutaneous adverse reactions
• Evidence supports a role for testing (in most countries) for ○ HLA-B*57:01 (abacavir) ○ HLA-B*15:02 (carbamazepine) ○ HLA-B*58:01 (allopurinol) • Evidence is lacking to support testing for other drugs, eg, beta lactams, nonsteroidal anti-inflammatory drugs

chemotherapeutic drug is not associated with increased rate of reactions and related rescue medication use during subsequent infusions.⁷¹ Similarly, a recent observational study suggests that premedication with antihistamines may not be necessary after the second infusion of cetuximab if patients did not develop any symptoms with the first 2 infusions.⁷²

Paclitaxel and the semisynthetic taxane docetaxel—associated immediate infusion reactions, usually during first or second exposure,⁷¹ are markedly reduced to 2% to 10% by premedication with corticosteroid and H1/H2 antihistamine.⁷³ The high proportion of immediate HSRs was supported by the complement activation property of Cremophor EL and polysorbate 80, solvents of paclitaxel and docetaxel, respectively.^{74,75} However, approximately 1% to 2% of patients had serious immediate HSRs despite premedication. Majority of the patients successfully resumed taxanes with increased premedication and slower rates of infusion or graded challenge, whereas few patients had more severe HSRs, including death.⁷⁶

Thus, the modified strategy for premedication (with reduced doses of dexamethasone and/or antihistamines or without any dose) on the first 2 infusions allows us to avoid unnecessary drug administration, steroid-related adverse effects, and potential medication errors with multiple sequential drug administrations. Whether similar strategies can be used safely for other monoclonal antibodies and chemotherapeutics needs to be studied further, given the heterogeneity of infusion reactions.

Perioperative anaphylaxis

There is no evidence supporting the use of premedication with antihistamines or corticosteroids to prevent perioperative anaphylaxis.^{20,33,35,77} It is generally accepted that antihistamines or corticosteroids will not mitigate IgE-mediated reactions.⁷⁸ Although evidence is only indirect,⁷⁹ guidelines indicate that the use of H1 antihistamines can be considered²⁰ or recommended³⁴ in cases where nonallergic histamine release is suspected. Slower administration of incremental doses of drugs associated with nonallergic histamine release such as opioids, NMBA, and vancomycin has also been proposed.³³ No evidence favoring premedication with a single dose of corticosteroids for preventing immediate HSRs was found.²⁰ Finally, in cases with ethylene oxide allergy, known to be difficult to completely avoid, premedication with antihistamines, corticosteroids, and omalizumab has been reported to be successful.^{80,81} The mainstay of prevention of perioperative anaphylaxis remains careful evaluation of prior unexplained perioperative anaphylaxis and proper avoidance in case of an allergy (especially for potential “hidden” allergens such as chlorhexidine or excipients).

Iodinated contrast media

Premedication before ICM administration has been used for decades although the evidence for its efficacy is almost absent. The rationale stems from the ability of ICMs to directly (without IgE) mediate basophil and mast cell degranulation.⁸¹⁻⁸³ The incidence was higher with the use of high-osmolar ionic monomers that have been abandoned, compared with the current low-osmolar nonionic ICMs.⁸² Premedication with H1- and/or H2-antihistamines could mitigate these histamine-mediated adverse effects. Corticosteroids exert an anti-inflammatory effect on various cells, including mast cells.⁸⁴ Most studies evaluating premedication in ICM-mediated iDHR using corticosteroids, H1-, H2-antihistamines, ephedrine, alone or in combination have methodological concerns.⁸⁵ Only 2 randomized, double-blind, placebo-controlled trials have been performed.^{86,87} Bertrand et al⁸⁶ evaluated hydroxyzine 100 mg versus placebo 2 hours before (a currently abandoned) ICM in patients without a prior iDHR, demonstrating a reduction of iDHR from 12.5% to 1% ($P < .0001$). Lasser et al⁸⁷ reported a reduction in iDHR using methylprednisolone 32 mg at 12 and 2 hours before ICM administration compared with placebo (1.7% vs 4.9%, $P = .005$). However, no significant reduction in patients experiencing moderate-to-severe iDHR was observed, and in those with a prior iDHR, no difference was reported. Premedication has not been shown to reduce the incidence of moderate-to-severe reactions or reaction-related deaths, and there is no evidence that premedication reduces incidence of iDHR in patients with a prior severe iDHR.⁸⁸ None of these studies included prior skin testing, as recommended currently by the EAACI.⁸⁹

Guidelines no longer support the routine administration of glucocorticoids and/or antihistamines to prevent anaphylaxis in patients with prior ICM DHR,³⁵ but recommend allergy evaluation

and identify safe alternatives in patients at risk,⁹⁰ or to consider premedication in the absence of alternatives although evidence for efficacy is lacking in these high-risk patients.⁹¹ The side effects of premedication with first-generation H1 antihistamines and corticosteroid,^{92,93} delay in radiological diagnosis, and prolonged hospitalization need to be weighed against the benefits.⁹⁴

Changing the ICM that resulted in the initial iDHR within the same class has been shown to be more effective than premedication in high-risk patients^{95,96} and has been included as a potential strategy in the ACR guidelines 10.3.⁹¹ However, the evidence is weak given the retrospective nature of the studies, absence of randomization, and absence of prior allergy evaluation. Moreover, it has been demonstrated that patients with immediate skin test positivity for the index ICM often have none or few of the other ICMs for which skin tests are positive. Alternative ICMs that are skin test negative are often tolerated^{46,47,51,85}; hence changing the type of ICM is an option.⁹⁷

We advise an elective allergy workup in those with a moderate-to-severe DHR to identify an immediate or non-immediate allergy, potential cross-reactive ICMs, and safe alternatives.^{47,49,50,89,97} A list of potentially cross-reactive ICMs for iDHR and niDHR and a diagnostic algorithm has been published by the EAACI.⁸⁹ For those in whom skin testing does not show evidence of an underlying allergy, an empirical change of ICM might further reduce the likelihood of recurrence of an iDHR,^{89,95,96} although additional prospective studies are warranted. For those with a prior iDHR who require urgent ICM administration, premedication could be used if no valid alternatives are available and the investigation is deemed necessary, along with vigilance for a potential severe repeat reaction. The role of premedication in niDHR has not been evaluated, and in case of proven ICM-mediated severe niDHR, strict avoidance remains mandatory.

Gadolinium-based contrast media

The incidence of GCM-induced DHR is considered lower compared with that observed with ICMs. GCM are not histamine releasers *in vitro*. Mostly, immediate isolated cutaneous reactions occur, although anaphylaxis and niDHR have been reported.⁴⁵ Premedication in primary prevention is considered unnecessary. However, similar to ICM, varying approaches exist for patients who have experienced a reaction.

First, premedication using H1 antihistamines and corticosteroids, analogous to protocols used for ICM premedication, has been applied in GCM-induced DHR. However, breakthrough reactions (BTRs) despite premedication occur frequently, and a recent meta-analysis suggested an incidence of 39% (95% confidence interval, 25%–48%).⁹⁸ In the same meta-analysis, no conclusion could be made regarding the effect of switching to an alternative GCM or using skin testing to prevent repeat reactions due to insufficient data. Empirical switching to an alternative GCM before readministration with or without premedication evaluated recently in a single-arm observational study⁹⁹ in 26 patients with mild-to-moderate DHR reduced the expected rate of BTRs to 3.7% (no control group was evaluated). No difference within those receiving no H1 antihistamine (diphenhydramine), or H1 antihistamine and corticosteroid premedication was observed, although groups were not proportional or randomized.

Secondly, evaluation for GCM-induced DHR via skin testing to identify subgroups with an underlying GCM allergy is being performed, largely by allergy specialist groups. In the largest

series to date, 18 of 132 (13.6%) patients with a potential GCM-induced DHR had positive skin tests, with most being diagnosed with an iDHR (95%).¹⁰⁰ All 6 patients with positive skin tests who were re-exposed to a negative skin-tested GCM tolerated the latter.

Premedication in patients with GCM-induced DHR is associated with frequent BTRs. Larger studies combining prior allergy workup, empirical switching to alternative GCM, and/or premedication are needed. For the present, a similar approach to ICM DHR is used for GCM DHR.

Clonal mast cell disorders

Patients with clonal mast cell disorders are at increased risk of anaphylaxis, theoretically during certain medical procedures, general anesthesia, and RCM administrations. The value of premedication is insufficiently studied in this population, and there is no evidence to support or refute premedication with antihistamines and corticosteroid before anesthesia in patients with mastocytosis. Many groups therefore advise premedication in this condition.⁴² For ICMs, observational data in mastocytosis are scarce.⁴² In 457 compiled patients with mastocytosis, 3 (0.6%) experienced an ICM-mediated iDHR, of which one was anaphylaxis.¹⁰¹ Conversely, in none of the patients experiencing fatal anaphylaxis after ICM exposure was mastocytosis identified (although only 8 of 34 cases underwent a bone marrow evaluation).¹⁰² Hermans et al¹⁰¹ suggested that patients with mastocytosis receiving ICM do not require premedication unless there is a history of ICM-mediated anaphylaxis or an anticipated high risk for anaphylaxis. However, larger studies are required to evaluate the use or burden of premedication in this specific patient group. The evidence for premedication is summarized in Table II.

RAPID DRUG DESENSITIZATION

Rapid drug desensitization (RDD) or temporary induction of drug tolerance induces a temporary state of tolerance to a medication responsible for HSRs. It is performed by gradual introduction of small amounts of medication in divided incremental steps over a short period of time (from several hours to a few days) until the total cumulative therapeutic dose is achieved and tolerated.^{103,104} RDD to BAs and chemotherapeutic agents is becoming standard of care, allowing a medication-allergic patient to receive the optimal agent particularly for cancers and rheumatologic disorders where standard therapies have been ineffective, associated with toxicities, or where no better alternatives are available.^{105,106}

RDD can be performed in both patients with IgE and non-IgE HSRs with similar success, despite different molecular mechanisms of DHR.¹⁰⁴ The principle of RDD is to abolish acute and late phase IgE-mediated activation of mast cell through delivering small, incremental drug doses usually beginning with 1:100,000 to 1/10 of the dose that does not cause nonspecific irritation when administered intradermally, and doubling the dose every 15 to 20 minutes until the full therapeutic dose is reached.^{107,108} The rationale for premedication depends on the nature of HSRs as well as the immune-inducing and chemical properties of each agent.¹⁰⁹

RDD has been shown to be an effective and safe method to reintroduce taxanes in patients with life-threatening HSRs. A non-IgE mechanism was initially postulated according to the result of nonspecific induction of histamine release from basophils in one study using paclitaxel alone (without Cremophor

TABLE II. Premedication

Prevention of drug hypersensitivity reactions
• Primary prevention: no role • Secondary prevention: in individuals with a previous hypersensitivity reaction
Chemotherapeutic agents and biologicals (monoclonal antibodies)
• Evidence supports a role for antihistamine (eg, diphenhydramine) and/or glucocorticoid (eg, dexamethasone) premedication in specific chemotherapy protocols, eg, cetuximab, paclitaxel, rituximab
Perioperative anaphylaxis
• Evidence is lacking to support the routine use of antihistamines and/or glucocorticoid premedication in patients with previous perioperative anaphylaxis or first episode exposure to perioperative agents
Radiocontrast media (RCM)
• Evidence is lacking to support the routine use of antihistamines and/or glucocorticoid premedication in patients receiving low- or iso-osmolar contrast material to prevent recurrent RCM anaphylaxis
Gadolinium-based contrast media (GCM)
• Evidence is lacking to support the routine use of antihistamines and/or glucocorticoid premedication in patients receiving GCM to prevent recurrent GCM anaphylaxis
Clonal mast cell disorders
• The value of premedication is insufficiently studied in this population and there is no evidence to support or refute premedication in patients with clonal mast cell disorders. Many groups however advise premedication in this condition

TABLE III. Rapid drug desensitization (RDD) or temporary induction of drug tolerance (TIDT)

Prevention of drug hypersensitivity reactions
• Primary prevention: no role • Secondary prevention: indicated in individuals with a previous immediate drug hypersensitivity reaction that may be IgE mediated or non-IgE mediated
Indication
• Evidence supports a role for prevention in hypersensitivity reactions to chemotherapeutic agents and biologicals (monoclonal antibodies), eg, taxane hypersensitivity reactions
No evidence
• Evidence does not support a role for RDD/TIDT in ◦ perioperative anaphylaxis ◦ radiocontrast media hypersensitivity ◦ gadolinium-based contrast media hypersensitivity

EL) in a patient with repeated HSRs after premedication and slowing the rate, and in healthy controls.¹¹⁰ However, some of these HSRs may be IgE mediated through demonstration of a positive immunoblot assay and skin test results, although predictive values of these skin test results remain to be verified.¹¹¹⁻¹¹³ Different protocols to approach taxane HSRs have been published; most authors have used skin testing and severity of initial HSRs for risk stratification. To maximize safety, reintroduction of taxanes in the high-risk group was initially offered through RDD, with an attempt to decelerate the protocol and resume regular infusion if patients have shown to tolerate RDD very well.^{113,114} With a standard protocol for RDD and premedication, approximately one-third of patients or 4% to 6% of RDD procedures had BTRs, usually with mild or grade 1

severity. Grade 2 or moderate-severe BTRs accounted for 4% to 6% of all patients receiving RDD. In patients with BTRs, the addition of aspirin 325 mg (oral) and montelukast 10 mg (oral) has been shown to be more effective at minimizing BTRs by inhibition of the synthesis of prostaglandins and blocking the receptor for cysteinyl leukotriene, respectively.¹¹⁵ These are important mediators secreted by activated mast cells and basophils. However, one study has questioned the benefit of this premedication regimen in taxane RDD, and this needs to be confirmed in a larger sample size.¹¹⁶ The evidence for rapid drug desensitization is summarized in Table III.

CONCLUSION

Prescreening using skin tests and intradermal tests identifies the putative and alternative drugs in perioperative anaphylaxis, ICM, and GCM iDHR. Pharmacogenomic tests using HLA-genotyping for high-risk drugs for SCAR are drug- and ethnicity-specific with variable cost-effectiveness depending on factors including the country's health care financing model and access to less costly alternative drugs. Premedication is effective in most iDHR to chemotherapeutic and BAs, but not for moderate-to-severe contrast media, and general anesthetic agent-induced HSRs. Desensitization is effective in IgE-mediated immune-mediated DHR and certain non-immune-mediated DHR such as some types of NSAID-HSRs.

REFERENCES

- Macy E. Immune-related adverse drug reactions and immunologically mediated drug hypersensitivity. *Immunol Allergy Clin North Am* 2020;40:635-47.
- Broyles AD, Banerji A, Barmettler S, Biggs CM, Blumenthal K, Brennan PJ, et al. Practical guidance for the evaluation and management of drug hypersensitivity: specific drugs. *J Allergy Clin Immunol Pract* 2020;8:116-116.
- Kuijper EC, French LE, Tensen CP, Vermeer MH, Bouwes Bavinck JN. Clinical and pathogenic aspects of the severe cutaneous adverse reaction epidermal necrolysis (EN). *J Eur Acad Dermatol Venereol* 2020;34:1957-71.
- Chang WC, Abe R, Anderson P, Anderson W, Ardern-Jones MR, Beachkofsky TM, et al. SJS/TEN 2019: from science to translation. *J Dermatol Sci* 2020;98:2-12.
- Regateiro FS, Marques ML, Gomes ER. Drug-induced anaphylaxis: an update on epidemiology and risk factors. *Int Arch Allergy Immunol* 2020;181:481-7.
- Castells M. Diagnosis and management of anaphylaxis in precision medicine. *J Allergy Clin Immunol* 2017;140:321-33.
- Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA, et al. International consensus on drug allergy. *Allergy* 2014;69:420-37.
- Légat L, Van Laere S, Nyssen M, Steurbaut S, Dupont AG, Cornu P. Clinical decision support systems for drug allergy checking: systematic review. *J Med Internet Res* 2018;20:e258.
- Rajan TV. The Gell-Coombs classification of hypersensitivity reactions: a re-interpretation. *Trends Immunol* 2003;24:376-9.
- Chung CH, Mirakhur B, Chan E, Le QT, Berlin J, Morse M, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose- α -1,3-galactose. *N Engl J Med* 2008;358:1109-17.
- Wong JT, Long A. Rituximab hypersensitivity: evaluation, desensitization, and potential mechanisms. *J Allergy Clin Immunol Pract* 2017;5:1564-71.
- Picard M. Management of hypersensitivity reactions to taxanes. *Immunol Allergy Clin North Am* 2017;37:679-93.
- Matucci A, Vultaggio A, Nencini F, Maggi E. Anaphylactic reactions to biological drugs. *Curr Opin Allergy Clin Immunol* 2020;20:346-51.
- Pagani M, Bavbek S, Dursun AB, Bonadonna P, Caralli M, Cernadas J, et al. Role of skin tests in the diagnosis of immediate hypersensitivity reactions to taxanes: results of a multicenter study. *J Allergy Clin Immunol Pract* 2019;7:990-7.
- Vultaggio A, Maggi E, Matucci A. Immediate adverse reactions to biologicals: from pathogenic mechanisms to prophylactic management. *Curr Opin Allergy Clin Immunol* 2011;11:262-8.
- Jönsson F, de Chaisemartin L, Granger V, Gouel-Chéron A, Gillis CM, Zhu Q, et al. An IgG-induced neutrophil activation pathway contributes to human drug-induced anaphylaxis. *Sci Transl Med* 2019;11:eaat1479.
- Muraro A, Lemanske RF Jr, Castells M, Torres MJ, Khan D, Simon HU, et al. Precision medicine in allergic disease—food allergy, drug allergy, and anaphylaxis—PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology. *Allergy* 2017;72:1006-21.
- Pichler WJ. Adverse side-effects to biological agents. *Allergy* 2006;61:912-20.
- Isabwe GAC, Garcia Neuer M, de Las Vecillas Sanchez L, Lynch DM, Marquis K, Castells M. Hypersensitivity reactions to therapeutic monoclonal antibodies: phenotypes and endotypes. *J Allergy Clin Immunol* 2018;142:159-70.
- Mertes PM, Malinovsky JM, Jouffroy L, Working Group of the SFAR and SFAAberer W, Terreehorst I, Brockow K, Demoly P, ENDA; EAACI Interest Group on Drug Allergy. Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. *J Investig Allergol Clin Immunol* 2011;21:442-53.
- Porri F, Lemiere C, Birnbaum J, Guilloux L, Lanteaume A, Didelot R, et al. Prevalence of muscle relaxant sensitivity in a general population: implications for a preoperative screening. *Clin Exp Allergy* 1999;29:72-5.
- Harper NJN, Cook TM, Garcez T, Farmer L, Floss K, Marinho S, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). *Br J Anaesth* 2018;121:159-71.
- Lobera T, Audicana MT, Pozo MD, Blasco A, Fernández E, Cañada P, et al. Study of hypersensitivity reactions and anaphylaxis during anesthesia in Spain. *J Investig Allergol Clin Immunol* 2008;18:350-6.
- Malinovsky JM, Decagny S, Wessel F, Guilloux L, Mertes PM. Systematic follow-up increases incidence of anaphylaxis during adverse reactions in anesthetized patients. *Acta Anaesthesiol Scand* 2008;52:175-81.
- Berboa F, Lafuente A, Javaloyes G, Cabrera-Freitag P, de la Borbolla JM, Moncada R, et al. The incidence of perioperative hypersensitivity reactions: a single-center, prospective, cohort study. *Anesth Analg* 2015;121:117-23.
- Savic LC, Kaura V, Yusaf M, Hammond-Jones AM, Jackson R, Howell S, et al. Incidence of suspected perioperative anaphylaxis: a multicenter snapshot study. *J Allergy Clin Immunol Pract* 2015;3:454-5.e1.
- Van Gasse AL, Sabato V, Degerbeck F, DeWitt AM, Oulkadi R, Faber MA, et al. Specific IgE to cefazolin: does it benefit diagnosis? *J Allergy Clin Immunol Pract* 2019;7:2932-4.
- Ebo DG, Faber M, Elst J, Van Gasse AL, Bridts CH, Mertens C, et al. In vitro diagnosis of immediate drug hypersensitivity during anesthesia: a review of the literature. *J Allergy Clin Immunol Pract* 2018;6:1176-84.
- Leysen J, Uytendaele A, Sabato V, Bridts CH, De Clerck LS, Ebo DG. Predictive value of allergy tests for neuromuscular blocking agents: tackling an unmet need. *Clin Exp Allergy* 2014;44:1069-75.
- Anderson J, Rose M, Green S, Fernando SL. The utility of specific IgE testing to chlorhexidine in the investigation of perioperative adverse reactions. *Ann Allergy Asthma Immunol* 2015;114:425-6.
- Fisher MM. The preoperative detection of risk of anaphylaxis during anaesthesia. *Anaesth Intensive Care* 2007;35:899-902.
- Garvey LH, Ebo DG, Mertes PM, Dewachter P, Garcez T, Kopac P, et al. An EAACI position paper on the investigation of perioperative immediate hypersensitivity reactions. *Allergy* 2019;74:1872-84.
- Kroigaard M, Garvey LH, Gillberg L, Johansson SG, Mosbech H, Florvaag E, et al. Scandinavian Clinical Practice Guidelines on the diagnosis, management and follow-up of anaphylaxis during anaesthesia. *Acta Anaesthesiol Scand* 2007;51:655-70.
- Laguna JJ, Archilla J, Doña I, Corominas M, Gastaminza G, Mayorga C, et al. Practical guidelines for perioperative hypersensitivity reactions. *J Investig Allergol Clin Immunol* 2018;28:216-32.
- Shaker MS, Wallace DV, Golden DBK, Oppenheimer J, Bernstein JA, Campbell RL, et al. Anaphylaxis—a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. *J Allergy Clin Immunol* 2020;145:1082-123.
- Chiriac AM, Tacquard C, Fadhel NB, Pellerin C, Malinovsky JM, Mertes PM, et al. Safety of subsequent general anaesthesia in patients allergic to neuromuscular blocking agents: value of allergy skin testing. *Br J Anaesth* 2018;120:1437-40.
- Guyon AC, Saff RR, Conroy M, Blumenthal KG, Camargo CA Jr, Long AA, et al. Comprehensive allergy evaluation is useful in the subsequent care of patients with drug hypersensitivity reactions during anesthesia. *J Allergy Clin Immunol Pract* 2015;3:94-100.
- Miller J, Clough SB, Pollard RC, Misbah SA. Outcome of repeat anaesthesia after investigation for perioperative anaphylaxis. *Br J Anaesth* 2018;120:1195-201.

39. Opstrup MS, Poulsen LK, Malling HJ, Jensen BM, Garvey LH. Dynamics of plasma levels of specific IgE in chlorhexidine allergic patients with and without accidental re-exposure. *Clin Exp Allergy* 2016;46:1090-8.
40. Bonadonna P, Pagani M, Aberer W, Bilò MB, Brockow K, Oude Elberink H, et al. Drug hypersensitivity in clonal mast cell disorders: ENDA/EACI position paper. *Allergy* 2015;70:755-63.
41. Fisher MM, Merefild D, Baldo B. Failure to prevent an anaphylactic reaction to a second neuromuscular blocking drug during anaesthesia. *Br J Anaesth* 1999;82:770-3.
42. Garvey LH, Ebo DG, Krøigaard M, Savic S, Clarke R, Cooke P, et al. The use of drug provocation testing in the investigation of suspected immediate peri-operative allergic reactions: current status. *Br J Anaesth* 2019;123:e126-34.
43. Brockow K. Immediate and delayed cutaneous reactions to radiocontrast media. *Chem Immunol Allergy* 2012;97:180-90.
44. Morcos SK. Review article: acute serious and fatal reactions to contrast media: our current understanding. *Br J Radiol* 2005;78:686-93.
45. Tasker F, Fleming H, McNeill G, Creamer D, Walsh S. Contrast media and cutaneous reactions. Part 1. Immediate hypersensitivity reactions to contrast media and gadolinium deposition. *Clin Exp Dermatol* 2019;44:839-43.
46. Brockow K, Romano A, Aberer W, Bircher AJ, Barbaud A, Bonadonna P, et al. Skin testing in patients with hypersensitivity reactions to iodinated contrast media—a European multicenter study. *Allergy* 2009;64:234-41.
47. Kim MH, Lee SY, Lee SE, Yang MS, Jung JW, Park CM, et al. Anaphylaxis to iodinated contrast media: clinical characteristics related with development of anaphylactic shock. *PLoS One* 2014;9:e100154.
48. Laroche D, Aimone-Gastin I, Dubois F, Huet H, Gérard P, Vergnaud MC, et al. Mechanisms of severe, immediate reactions to iodinated contrast material. *Radiology* 1998;209:183-90.
49. Schrijvers R, Breynaert C, Ahmedali Y, Bourrain JL, Demoly P, Chiriac AM. Skin testing for suspected iodinated contrast media hypersensitivity. *J Allergy Clin Immunol Pract* 2018;6:1246-54.
50. Lee JH, Kwon OY, Park SY, Seo B, Won HK, Kang Y, et al. Validation of the prescreening intradermal skin test for predicting hypersensitivity to iodinated contrast media: a prospective study with ICM challenge. *J Allergy Clin Immunol Pract* 2020;8:267-72.
51. Caimmi S, Benyahia B, Suau D, Bousquet-Rouanet L, Caimmi D, Bousquet PJ, et al. Clinical value of negative skin tests to iodinated contrast media. *Clin Exp Allergy* 2010;40:805-10.
52. Prieto-García A, Tomás M, Pineda R, Tornero P, Herrero T, Fuentes V, et al. Skin test-positive immediate hypersensitivity reaction to iodinated contrast media: the role of controlled challenge testing. *J Investig Allergol Clin Immunol* 2013;23:183-9.
53. Yoon SH, Lee SY, Kang HR, Kim JY, Hahn S, Park CM, et al. Skin tests in patients with hypersensitivity reaction to iodinated contrast media: a meta-analysis. *Allergy* 2015;70:625-37.
54. Castells MC. Drug allergy: phenotypes, endotypes, and biomarkers. *J Allergy Clin Immunol Pract* 2017;5:626-7.
55. Chang CJ, Chen CB, Hung SI, Ji C, Chung WH. Pharmacogenetic testing for prevention of severe cutaneous adverse drug reactions. *Front Pharmacol* 2020;11:969.
56. Garon SL, Pavlos RK, White KD, Brown NJ, Stone CA Jr, Phillips EJ. Pharmacogenomics of off-target adverse drug reactions. *Br J Clin Pharmacol* 2017;83:1896-911.
57. Oussalah A, Yip V, Mayorga C, Blanca M, Barbaud A, Nakonechna A, et al. Task Force “Genetic predictors of drug hypersensitivity” of the European Network on Drug Allergy (ENDA), European Academy of Allergy and Clinical Immunology (EAACI). Genetic variants associated with T cell-mediated cutaneous adverse drug reactions: a PRISMA-compliant systematic review—an EAACI position paper. *Allergy* 2020;75:1069-98.
58. Zhou Y, Krebs K, Milani L, Lauschke VM. Global frequencies of clinically important HLA alleles and their implications for the cost-effectiveness of preemptive pharmacogenetic testing. *Clin Pharmacol Ther* 2021;109:160-74.
59. Doña I, Pérez-Sánchez N, Eguiluz-García I, Muñoz-Cano R, Bartra J, Torres MJ, et al. Progress in understanding hypersensitivity reactions to nonsteroidal anti-inflammatory drugs. *Allergy* 2020;75:561-75.
60. Lee JU, Park JS, Chang HS, Park CS. Complementary participation of genetics and epigenetics in development of NSAID-exacerbated respiratory disease. *Allergy Asthma Immunol Res* 2019;11:779-94.
61. Jurado-Escobar R, Perkins JR, García-Martín E, Isidoro-García M, Doña I, Torres MJ, et al. Update on the genetic basis of drug hypersensitivity reactions. *J Investig Allergol Clin Immunol* 2017;27:336-45.
62. Nicoletti P, Carr DF, Barrett S, McEvoy L, Friedmann PS, Shear NH, et al. Beta-lactam-induced immediate hypersensitivity reactions: a genome-wide association study of a deeply phenotyped cohort. *J Allergy Clin Immunol* 2020;S0091-6749(20):31405-6.
63. Durham CG, Thotakura D, Sager L, Foster J, Herrington JD. Cetirizine versus diphenhydramine in the prevention of chemotherapy-related hypersensitivity reactions. *J Oncol Pharm Pract* 2019;25:1396-401.
64. Siena S, Glynne-Jones R, Thaler J, Adenis A, Preusser P, Aranda Aguilar E, et al. Infusion-related reactions (IRR) associated with cetuximab plus irinotecan treatment in patients with irinotecan-resistant metastatic colorectal cancer (mCRC): findings from the MABEL study. *J Clin Oncol* 2007;25:18(suppl): Abstract 4137.
65. Colombel JF, Loftus EV Jr, Tremaine WJ, Egan LJ, Harmsen WS, Schleck CD, et al. The safety profile of infliximab in patients with Crohn’s disease: the Mayo clinic experience in 500 patients. *Gastroenterology* 2004;126:19-31.
66. Sany J, Kaiser MJ, Jorgensen C, Trape G. Study of the tolerance of infliximab infusions with or without betamethasone premedication in patients with active rheumatoid arthritis. *Ann Rheum Dis* 2005;64:1647-9.
67. Vultaggio A, Matucci A, Parronchi P, Rossi O, Palandri F, Romagnani S, et al. Safety and tolerability of infliximab therapy: suggestions and criticisms based on wide clinical experience. *Int J Immunopathol Pharmacol* 2008;21:367-74.
68. Vogel WH. Infusion reactions: diagnosis, assessment, and management. *Clin J Oncol Nurs* 2010;14:E10-21.
69. Lin S, Lucas MS, Heerema NA, Matkovich JJ, Moran ME, Cheney C, et al. A Phase II study of the TNF- α inhibitor etanercept and thrice weekly rituximab in relapsed CLL/SLL: clinical activity in the absence of del(17p13) genomic abnormalities. *Blood* 2006;108:804A.
70. Eason JD, Pascual M, Wee S, Farrell M, Phelan J, Boskovic S, et al. Evaluation of recombinant human soluble dimeric tumor necrosis factor receptor for prevention of OKT3-associated acute clinical syndrome. *Transplantation* 1996; 61:224-8.
71. Berger MJ, Vargo C, Vincent M, Shaver K, Phillips G, Layman R, et al. Stopping paclitaxel premedication after two doses in patients not experiencing a previous infusion hypersensitivity reaction. *Support Care Cancer* 2015;23: 2019-24.
72. Timoney J, Chung KY, Park V, Trocola R, Peake C, Saltz LB. Cetuximab use without chronic antihistamine premedication. *J Clin Oncol* 2006;24(suppl): Abstract 13521.
73. Markman M, Kennedy A, Webster K, Kulp B, Peterson G, Belinson J. Paclitaxel-associated hypersensitivity reactions: experience of the gynecologic oncology program of the Cleveland Clinic Cancer Center. *J Clin Oncol* 2000; 18:102-5.
74. Szebeni J, Muggia FM, Alving CR. Complement activation by Cremophor EL as a possible contributor to hypersensitivity to paclitaxel: an in vitro study. *J Natl Cancer Inst* 1998;90:300-6.
75. Weiszhar Z, Czucz J, Révész C, Rosivall L, Szebeni J, Rozsnyay Z. Complement activation by polyethoxylated pharmaceutical surfactants: Cremophor-EL, Tween-80 and Tween-20. *Eur J Pharm Sci* 2012;45:492-8.
76. Weiss RB, Donehower RC, Wiernik PH, Ohnuma T, Gralla RJ, Trump DL, et al. Hypersensitivity reactions from taxol. *J Clin Oncol* 1990;8:1263-8.
77. Harper NJ, Dixon T, Dugué P, Edgar DM, Fay A, Gooi HC, et al. Working Party of the Association of Anaesthetists of Great Britain and Ireland. Suspected anaphylactic reactions associated with anaesthesia. *Anaesthesia* 2009; 64:199-211.
78. Setlock MA, Cotter TP, Rosner D. Latex allergy: failure of prophylaxis to prevent severe reaction. *Anesth Analg* 1993;76:650-2.
79. Xiang Z, Yan-Liang Q, Xiao-Yang S, Yan-Hui Z, Min C, Guo-Shen G, et al. Effects of promethazine or dexamethasone pretreatment on mivacurium-induced histamine release in children. *Paediatr Anaesth* 2014;24:322-6.
80. Bilò MB, Corsi A, Brianzoni MF, Garritani MS, Antonicelli L. Efficacy of a single dose of omalizumab for the prevention of ethylene oxide intraoperative anaphylaxis. *Ann Allergy Asthma Immunol* 2018;121:249-50.
81. Assem ES, Bray K, Dawson P. The release of histamine from human basophils by radiological contrast agents. *Br J Radiol* 1983;56:647-52.
82. Peachell PT, Morcos SK. Effect of radiographic contrast media on histamine release from human mast cells and basophils. *Br J Radiol* 1998;71:24-30.
83. Stellato C, de Crescenzo G, Patella V, Mastroradi P, Mazzarella B, Marone G. Human basophil/mast cell releasability. XI. Heterogeneity of the effects of contrast media on mediator release. *J Allergy Clin Immunol* 1996;97:838-50.
84. Scheschowitz K, Leite JA, Assreuy J. New insights in glucocorticoid receptor signaling—more than just a ligand-binding receptor. *Front Endocrinol (Lausanne)* 2017;8:16.
85. Schrijvers R, Demoly P, Chiriac AM. Premedication for iodinated contrast media induced immediate hypersensitivity reactions. *Curr Treat Options Allergy* 2019;6:538-53.
86. Bertrand PR, Soyer PM, Rouleau PJ, Alison DP, Billardon MJ. Comparative randomized double-blind study of hydroxyzine versus placebo as premedication before injection of iodinated contrast media. *Radiology* 1992;184:383-4.

87. Lasser EC, Berry CC, Mishkin MM, Williamson B, Zheutlin N, Silverman JM. Pretreatment with corticosteroids to prevent adverse reactions to nonionic contrast media. *AJR Am J Roentgenol* 1994;162:523-6.
88. Tramèr MR, von Elm E, Loubeyre P, Hauser C. Pharmacological prevention of serious anaphylactic reactions due to iodinated contrast media: systematic review. *BMJ* 2006;333:675.
89. Torres MJ, Trautmann A, Böhm I, Scherer K, Barbaud A, Bavbek S, et al. Practice parameters for diagnosing and managing iodinated contrast media hypersensitivity. *Allergy* 2021;76:1325-39.
90. European Society of Urogenital Radiology. ESUR Guidelines on Contrast Agents version 10.0. Available from: http://www.esur.org/fileadmin/content/2019/ESUR_Guidelines_10.0_Final_Version.pdf. Accessed February 20, 2021.
91. American College of Radiology Committee on Drugs and Contrast Media. ACR Manual; 2021. Available from: https://www.acr.org/-/media/ACR/files/clinical-resources/contrast_media.pdf. Accessed February 20, 2021.
92. Mervak BM, Davenport MS, Ellis JH, Cohan RH. Rates of breakthrough reactions in inpatients at high risk receiving premedication before contrast-enhanced CT. *AJR Am J Roentgenol* 2015;205:77-84.
93. Waljee AK, Rogers MA, Lin P, Singal AG, Stein JD, Marks RM, et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. *BMJ* 2017;357:j1415.
94. Davenport MS, Mervak BM, Ellis JH, Dillman JR, Dunnick NR, Cohan RH. Indirect cost and harm attributable to oral 13-hour inpatient corticosteroid prophylaxis before contrast-enhanced CT. *Radiology* 2016;279:492-501.
95. Abe S, Fukuda H, Tobe K, Ibukuro K. Protective effect against repeat adverse reactions to iodinated contrast medium: premedication vs. changing the contrast medium. *Eur Radiol* 2016;26:2148-54.
96. Park HJ, Park JW, Yang MS, Kim MY, Kim SH, Jang GC, et al. Re-exposure to low osmolar iodinated contrast media in patients with prior moderate-to-severe hypersensitivity reactions: a multicentre retrospective cohort study. *Eur Radiol* 2017;27:2886-93.
97. Kwon OY, Lee JH, Park SY, Seo B, Won HK, Kang Y, et al. Novel strategy for the prevention of recurrent hypersensitivity reactions to radiocontrast media based on skin testing. *J Allergy Clin Immunol Pract* 2019;7:2707-13.
98. Walker DT, Davenport MS, McGrath TA, McInnes MDF, Shankar T, Schieda N. Breakthrough hypersensitivity reactions to gadolinium-based contrast agents and strategies to decrease subsequent reaction rates: a systematic review and meta-analysis. *Radiology* 2020;296:312-21.
99. Walker D, McGrath TA, Glikstein R, Chakraborty S, Blanchette C, Schieda N. Empiric switching of gadolinium-based contrast agents in patients with history of previous immediate hypersensitivity reaction to GBCA: a prospective single-center, single-arm efficacy trial. *Invest Radiol* 2021;56:369-73.
100. Mankouri F, Gauthier A, Srisuwatthari W, Moutou A, Borushko A, Popa L, et al. Hypersensitivity to gadolinium-based contrast agents: a single-center retrospective analysis over 7 years. *J Allergy Clin Immunol Pract* 2021;9:1746-1749.e2.
101. Hermans MAW, Arends NJT, Gerth van Wijk R, van Hagen PM, Kluin-Nelemans HC, Oude Elberink HNG, et al. Management around invasive procedures in mastocytosis: an update. *Ann Allergy Asthma Immunol* 2017;119:304-9.
102. Palmiere C, Reggiani Bonetti L. Risk factors in fatal cases of anaphylaxis due to contrast media: a forensic evaluation. *Int Arch Allergy Immunol* 2014;164:280-8.
103. Cernadas JR, Brockow K, Romano A, Aberer W, Torres MJ, Bircher A, et al. General considerations on rapid desensitization for drug hypersensitivity—a consensus statement. *Allergy* 2010;65:1357-66.
104. Castells M, Sancho-Serra Mdel C, Simarro M. Hypersensitivity to antineoplastic agents: mechanisms and treatment with rapid desensitization. *Cancer Immunol Immunother* 2012;61:1575-84.
105. Castells MC, Tennant NM, Sloane DE, Hsu FI, Barrett NA, Hong DI, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol* 2008;122:574-80.
106. Madrigal-Burgaleta R, Bernal-Rubio L, Berges-Gimeno MP, Carpio-Escalona LV, Gehlhaar P, Alvarez-Cuesta E. A large single-hospital experience using drug provocation testing and rapid drug desensitization in hypersensitivity to antineoplastic and biological agents. *J Allergy Clin Immunol Pract* 2019;7:618-32.
107. Sancho-Serra Mdel C, Simarro M, Castells M. Rapid IgE desensitization is antigen specific and impairs early and late mast cell responses targeting FcεRI internalization. *Eur J Immunol* 2011;41:1004-13.
108. Limsuwan T, Castells MC. Outcomes and safety of rapid desensitization for chemotherapy hypersensitivity. *Expert Opin Drug Saf* 2010;9:39-53.
109. Picard M, Castells MC. Re-visiting hypersensitivity reactions to taxanes: a comprehensive review. *Clin Rev Allergy Immunol* 2015;49:177-91.
110. Essayan DM, Kagey-Sobotka A, Colarusso PJ, Lichtenstein LM, Ozols RF, King ED. Successful parenteral desensitization to paclitaxel. *J Allergy Clin Immunol* 1996;97:42-6.
111. Prieto García A, Pineda de la Losa F. Immunoglobulin E-mediated severe anaphylaxis to paclitaxel. *J Investig Allergol Clin Immunol* 2010;20:170-1.
112. Madrigal-Burgaleta R, Berges-Gimeno MP, Angel-Pereira D, Ferreiro-Monteagudo R, Guillen-Ponce C, Pueyo C, et al. Hypersensitivity and desensitization to antineoplastic agents: outcomes of 189 procedures with a new short protocol and novel diagnostic tools assessment. *Allergy* 2013;68:853-61.
113. Picard M, Pur L, Caiado J, Giavina-Bianchi P, Galvão VR, Berlin ST, et al. Risk stratification and skin testing to guide re-exposure in taxane-induced hypersensitivity reactions. *J Allergy Clin Immunol* 2016;137:1154-64.
114. Alvarez-Cuesta E, Madrigal-Burgaleta R, Angel-Pereira D, Ureña-Tavera A, Zamora-Verduga M, Lopez-Gonzalez P, et al. Delving into cornerstones of hypersensitivity to antineoplastic and biological agents: value of diagnostic tools prior to desensitization. *Allergy* 2015;70:784-94.
115. Breslow RG, Caiado J, Castells MC. Acetylsalicylic acid and montelukast block mast cell mediator-related symptoms during rapid desensitization. *Ann Allergy Asthma Immunol* 2009;102:155-60.
116. Lopez-Gonzalez P, Madrigal-Burgaleta R, Carpio-Escalona LV, Bernal-Rubio L, Guerra E, Berges-Gimeno MP, et al. Assessment of antihistamines and corticosteroids as premedication in rapid drug desensitization to paclitaxel: outcomes in 155 procedures. *J Allergy Clin Immunol Pract* 2018;6:1356-62.