



Management and Prevention of Hypersensitivity Reactions to Radiocontrast Media: A Consensus Statement from the American College of Radiology and the American Academy of Allergy, Asthma & Immunology

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Intravenous iodinated contrast media (ICM) is widely used in the United States, and it is imperative to provide guidance on the management of adverse reactions to ICM as well as the preparation, planning, and potential premedication for patients with previous reactions. Currently there is a discordance between the American College of Radiology Contrast Manual, which recommends premedication to prevent repeat hypersensitivity reactions to ICM, and the Anaphylaxis 2020 Practice Parameters Update, which recommends against routine administration of glucocorticoids and/or antihistamines to prevent anaphylaxis with prior ICM hypersensitivity reactions. A task force of experts from radiology who are also members of the American College of Radiology Committee on Drugs and Contrast Media and expert allergists/immunologists including members of the Adverse Reactions to Drugs, Biologics and Latex Committee of American Academy of Allergy, Asthma & Immunology evaluated the scientific evidence to develop consensus recommendations that are endorsed by both organizations. The task force took into account the strength of evidence and balanced the potential risks of recurrent reactions with those of premedication and product avoidance when making these recommendations to improve and standardize the care of patients who experience or have a history of reaction to ICM.

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Introduction

Intravenous iodinated contrast media (ICM) is widely used across the United States. Eighty million CT scans were performed in the United States in 2019, an estimated 37.5% of which used ICM.^{1,2} Adverse reactions to ICM can occur immediately after exposure or may be delayed. Reactions have decreased in incidence as high-osmolality contrast media (HOCM) have been replaced by low-osmolality contrast media (LOCM), with current rates of acute reactions reported at 0.2% to 0.7%.³⁻⁶ However, it remains imperative to provide guidance on the management of immediate and delayed reactions to ICM as well as the preparation, planning, and potential premedication for patients who have experienced adverse reactions. Patients labeled as having an ICM allergy in the medical record pose a multidisciplinary clinical problem requiring health care professionals to obtain a comprehensive history and to balance the potential risks of recurrent reactions with those of premedication and product avoidance, as appropriate. A consequence is the increased use of glucocorticoid prophylaxis. Currently there is a discordance between the American College of Radiology (ACR) Contrast Manual, which recommends premedication to prevent repeat hypersensitivity reactions (HSRs) in patients with a prior reaction to ICM, and the Anaphylaxis 2020 Practice Parameters Update, which recommends against routine administration of glucocorticosteroids and/or antihistamines to prevent anaphylaxis in patients with prior ICM HSRs. Notably, this was a conditional recommendation with a low certainty rating of evidence.^{7,8} Although there are standardized regimens, discrepancies

exist between allergy/immunology and radiology practices, as well as between European and North American recommendations.⁷⁻⁹ In addition, whereas the ACR Manual mentions that switching contrast media within the same class may help reduce the likelihood of a subsequent contrast reaction, the Anaphylaxis Practice Parameters do not discuss this strategy.

As evidence continues to evolve, there are persistent gaps between clinical care based on best evidence and normative care observed in clinical practice.¹⁰ In addition, many myths persist related to ICM, such as an association with iodine and shellfish. To address these gaps, we convened a multidisciplinary task force of allergy/immunology physician representatives with ICM expertise from the American Academy of Allergy, Asthma & Immunology (AAAAI) and radiology physician representatives from the ACR Committee on Drugs and Contrast to evaluate the latest scientific evidence and develop consensus recommendations to guide ordering providers, allergy/immunology physicians, and radiologists in the use of contrast media and the prevention and management of contrast-associated reactions. This document contains joint statements endorsed by the ACR and AAAAI to improve and standardize the care of patients who experience or have a history of an adverse reaction to ICM. High-quality evidence and methodologically rigorous studies are lacking. Therefore, these recommendations should not be taken as definitive standards of practice because they may be subject to change as additional evidence becomes available. Although risk reduction strategies detailed here have been

Summary

Key outcomes from a multidisciplinary task force on hypersensitivity reactions to iodinated contrast media include recommendations to document reactions thoroughly in the electronic health record, including symptoms and the specific inciting agent, and a discussion of varying strategies for avoidance of repeat acute hypersensitivity reactions to iodinated contrast media according to the severity of the index reaction; importantly, no corticosteroid premedication is generally recommended for patients with a prior mild acute hypersensitivity reaction.

Essentials

- Documentation of iodinated contrast media (ICM) hypersensitivity reactions, including symptoms and the specific inciting agent in the electronic medical record, is recommended to optimize future ICM reaction management.
- High-quality evidence and methodologically rigorous studies are lacking owing to: (a) the rarity of moderate and severe reactions to low-osmolality iodinated contrast agents; (b) the paucity of methodologically sound studies; and (c) the heterogeneity of published studies, including the multiplicity of premedication and skin testing regimens, variations in patient selection for premedication, and differing contrast agents used in switching methodology.
- For patients with a history of mild immediate ICM hypersensitivity reactions, premedication is not recommended; this is a change from prior American College of Radiology recommendations. Switching the contrast agent is recommended when the inciting agent(s) is known and when feasible.
- For patients with a history of severe immediate ICM hypersensitivity reactions, it is recommended first to consider alternative imaging studies. If there is no acceptable alternative study that does not entail exposure to the same class of contrast, premedication is recommended and switching the contrast agent is recommended when feasible; this is a change from the most recent Joint Task Force Practice Parameters on Anaphylaxis. The study should be performed in a hospital setting with a rapid response team available, including personnel, equipment, and supplies to treat anaphylaxis.
- No premedication is necessary for patients with prior chemotoxic or physiologic reactions or an isolated history of shellfish allergy or iodine allergy including topical povidone-iodine.

Keywords

Contrast allergy, Contrast hypersensitivity, Iodinated contrast allergy, Iodinated contrast hypersensitivity, Anaphylaxis, Contrast skin testing, Contrast switching, Contrast reaction, Delayed contrast reaction, Immediate contrast reaction

shown to be efficacious for reducing the frequency and severity of HSRs in prior reactors, serious reactions may still occur. Also, individuals who are not prior reactors are also at risk for iodinated contrast reactions. For these reasons, all imaging centers should be prepared to manage an adverse contrast reaction related to the administration of intravenous contrast material in any patient regardless of the history of a prior adverse reaction and should include personnel, equipment, and supplies to treat anaphylaxis. This includes adequate training of all personnel who may be involved in the care of the patient as it relates to contrast reaction management, such as the technologist, radiologist, and any nursing staff according to their scope of practice.

Methodology

Task Force Composition

The task force consisted of five representatives from the ACR and five from the AAAAI, who have specialized expertise in adverse reactions to ICM. All radiology members of the task force are

practicing radiologists and members of the ACR Committee on Drugs and Contrast Media and have collectively authored 39 peer-reviewed journal articles related to intravenous ICM, adverse reactions to contrast media, or contrast reaction management. The AAAAI representatives include practicing allergists/immunologists who are known experts in the field, and who are also members of the AAAAI Adverse Reaction to Drugs, Biologics, and Latex Committee (A.R., M.K., A.C., and R.S.), who collectively have authored 35 relevant publications. None of the authors have relevant financial conflicts of interest.

Literature Review

An initial literature review was performed of PubMed with the search terms (Iodinated Contrast Media) AND ((contrast reaction) OR (allergic[keyword] AND iodinated contrast media) OR (contrast AND (premedication AND reaction))), (Skin testing OR Patch testing OR skin prick testing OR Contrast challenge) AND (Severe cutaneous adverse reaction OR Anaphylaxis OR Immediate reaction OR IgE-mediated reaction OR Stevens Johnson Syndrome OR Toxic Epidermal Necrolysis OR Acute Generalized Exanthematous pustulosis OR Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)). The results of the literature search was divided among the members of the task force, who reviewed the titles and abstracts, identified relevant articles, and added references that were also applicable. If there was a question about relevance, this was brought to the larger group for reconciliation. The articles relevant to each subsection were reviewed in full by the authors who initially drafted those subsections (each subsection was assigned to a two-person team of a radiologist and an allergist). All articles that were relevant to the recommendations listed in the supplemental material were initially reviewed for study quality per trained ACR staff and then the full articles were reviewed for completeness and validity independently by all authors.

Strength of Evidence Evaluation of Literature

The study quality and strength of evidence were determined following the ACR Appropriateness Criteria Evidence Document.¹¹ A concise adaptation of the Evidence document for grading an example study is provided in Supplemental Appendices A and B of that document; however, we recommend that reader refer to the full document for further details of this structured approach, which was developed using the principles of Grading of Recommendations, Assessment, Development, and Evaluations and the National Academy of Medicine Institute of Medicine Trustworthy Guideline standards.

Recommendation Development

Common clinical scenarios related to ICM HSRs were considered by the task force and recommendations were proposed based on the literature review of the topic and the relative strength of the evidence. The task force limited the recommendations to intravenous ICM administration, which was the focus of the literature review, excluding intraarterial, intrathecal, enteric, and intra-articular injections, and excluded consideration of contrast material classes other than ICM (eg, gadolinium-based contrast agents or ultrasound contrast agents). The task force also considered the balance between the potential for benefit compared with the potential for harm or burden relevant for the decision to

recommend premedication versus no premedication or contrast avoidance (more specifically, balancing the risk of recurrent iodinated contrast reactions and direct and indirect adverse effects of premedication, in the context of considering the low-quality nature of studies designed to assess reaction prevention). The practicality and feasibility of the recommendation in real-world radiology practice were also debated. After structured discussions in which all stakeholders shared perspectives and explored options, we achieved recommendations via unanimous consensus of task force members.

Definitions, Classification, and Documentation

For this document, we rely on terminology outlined in a recent AAAAI (EHR) documentation workgroup report, Anaphylaxis and Drug Allergy Practice Parameters. Broadly, the term “adverse reaction” to ICM encompasses various subcategories including immediate reactions (occurring within 1 hour of administration) regardless of whether these are IgE-mediated or non-IgE mediated, delayed (occurring more than 1 hour after administration), nephrotoxic, hemodynamic fluid shift, and others such as extravasation.^{9,12,13}

An adverse drug reaction includes unintended effects of a drug that occur owing to its inherent pharmacologic properties.^{12,13} Drug HSRs are immune-mediated adverse reactions that can be immediate in onset (within 1 hour) or delayed (more than 1 hour).^{14,15} Symptoms of immediate-onset HSR, including hypotension, tachycardia, bradycardia, and bronchoconstriction, can all occur after the administration of ICM through other mechanisms. It may be difficult to determine whether a reaction is an immune-mediated response to ICM or has another underlying cause. Thus, it is important for the treating health care professional to document all symptoms and the time of onset of the reactions¹⁶ in the EHR allergy field or module. This information, including the reaction treatment and monitoring time, may also be included in the radiology report if workflow permits. If there is uncertainty, symptoms should be treated as a drug HSR in the acute response and further evaluation by an allergist may be helpful once the patient is stable.

Throughout this report, we will refer to immediate ICM HSRs and delayed ICM HSRs as immediate reactions and delayed reactions, respectively. When we discuss premedication throughout the document, we are referring to glucocorticosteroids with or without antihistamine, which is reflective of the variable use of antihistamines within premedication regimens in the literature.

Immediate Reactions

Epidemiology of Immediate Reactions

Immediate reactions to LOCM and iso-osmolar contrast media have been reported to occur in 0.3% to 1.4% of injections and are most commonly mild (0.2% to 0.5%) or moderate (0.04% to 0.1%) in severity.^{5,17–20} Reports of severe reactions (0.005% to 0.06%) are uncommon, as are fatalities (0.0006%).^{17,18,21}

Pathophysiology

Controversy persists regarding the pathogenesis for immediate reactions to ICM. In most patients, these reactions are non-IgE

mediated, although IgE-mediated reactions also occur.²² The symptoms of non-IgE mediated reactions are suspected to result from mediator release from mast cells and basophils owing to the nonspecific binding of contrast to membrane receptors, the osmolality effect of the contrast media, or indirectly by complement-kinin activation.^{23–25} Reports of positive skin tests with nonirritating concentrations of ICM support an IgE-mediated pathogenesis for some reactions, particularly severe ones.^{26,27} Skin testing (ST) is more likely to be positive in severe reactions, particularly life-threatening ones with cardiovascular symptoms.^{26,28,29}

Identifying and Grading Immediate Reactions

Immediate reactions are referred to in the ACR Manual on Contrast Media⁷ as allergic-like, based on heterogeneous mechanisms, and categorized as mild, moderate, or severe. Mild reactions are characterized by self-limited, nonprogressive symptoms (Table 1). Moderate reactions exhibit signs and symptoms that are more pronounced than mild reactions but do not result in altered vital signs (eg, generalized urticaria). These reactions commonly require medical management with the potential to become severe if not treated.⁷

Severe reactions have signs and symptoms that are often life-threatening and can result in permanent morbidity or death if not managed appropriately. Severe reactions include symptoms fulfilling the criteria for anaphylaxis, as discussed subsequently.

Other non-immune mediated adverse reactions or intolerances (synonymous with physiologic reactions) are reactions that generally do not require treatment (eg, isolated nausea or vomiting with no other systemic symptoms, chills or a sensation of warmth, headaches, altered sense of taste, dizziness or lightheadedness without hypotension) as well as reactions that may require attention by appropriately trained medical personnel (eg, vasovagal reactions, panic reactions, hypertension, chest pain, arrhythmias, and seizures).⁷ These physiologic reactions do not require premedication for future ICM administrations because they are non-immune mediated adverse reactions.

Treatment of mild or moderate immediate reactions and non-immune mediated reactions varies depending on the patient's symptoms and clinical circumstances. Specific recommendations are beyond the scope of this document, and potential treatment algorithms can be found in the ACR Contrast Manual.⁷

Anaphylaxis

Anaphylaxis is a specific terminology with accepted criteria well known in the allergy/immunology literature that is not as well defined in radiology literature. A summary is given next.

Clinical symptoms.

Anaphylaxis is an acute life-threatening systemic allergic reaction. The National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network published anaphylaxis diagnosis criteria in 2006, and this definition remains the most widely accepted current framework. The ACR Contrast Manual does not specifically address the criteria for anaphylaxis and refers to hypotension with tachycardia as an “anaphylactoid reaction.” The formal definition applies to all allergens including ingested medications or food exposure, which is why the

Table 1: Categories of Acute Reactions to Iodinated Contrast Media Adapted from American College of Radiology Contrast Manual⁷

Type of Adverse Reaction	Severity	Physical Findings	Vital Signs
Hypersensitivity	Mild	Localized urticaria or pruritic, or few scattered hives	Normal
Hypersensitivity	Mild	Sensation of itchy or scratchy throat	Normal
Hypersensitivity	Mild	Nasal congestion, sneezing, conjunctivitis, rhinorrhea	Normal
Hypersensitivity	Moderate	Diffuse, rapid spreading urticaria (ie, $\geq 50\%$ body surface area)	Normal
Hypersensitivity	Moderate	Facial angioedema	Normal
Hypersensitivity	Moderate	Throat tightness or hoarseness	Normal
Hypersensitivity	Moderate	Wheezing/bronchospasm	Normal
Hypersensitivity	Severe	Facial angioedema with dyspnea	Hypoxia
Hypersensitivity	Severe	Throat tightness or hoarseness (laryngeal edema) with or without stridor	Hypoxia
Hypersensitivity	Severe	Wheezing or bronchospasm	Hypoxia
Hypersensitivity	Severe	Hypotension	Tachycardia
Hypersensitivity	Severe	Systemic reaction involving two or more of moderate symptoms listed earlier*	May be normal or altered
Nonallergic	Mild	Limited nausea or vomiting	Normal
Nonallergic	Mild	Isolated flushing, warmth, or chills	Normal
		Headache, anxiety, or altered taste	Normal
		Subjective dizziness	Normal
Nonallergic	Mild or Moderate (if not self-limiting)	Vasovagal reaction (hypotension)	Bradycardia
Nonallergic	Moderate	Chest pain	Normal
Nonallergic	Severe	Arrhythmia	Normal
Nonallergic	Severe	Convulsions or seizure	Normal
Nonallergic	Severe	Hypertensive emergency	Hypertensive with end-organ ischemia symptoms

* Systemic symptoms refer to involvement of any other body systems in addition to the system mentioned.

onset could occur up to hours later. However, for our purposes we will adapt the formal definition as it applies to intravenously administered ICM.

Anaphylaxis to ICM should be considered when the acute onset of illness occurs within minutes after intravenous ICM administration and in the absence of other known allergens or triggers. In such situations, anaphylaxis is considered likely if any two or more of these criteria are met:

- Involvement of skin or mucosal tissue, or both.
- Respiratory compromise.
- Reduced blood pressure or associated symptoms of end-organ dysfunction. (Note that severe hypotension may preclude the manifestation of any other anaphylaxis symptoms, and anaphylaxis should be considered when there is no other source for the acute onset of severe hypotension within minutes of intravenous ICM administration [eg, shock, sepsis, or vasovagal reaction] [Table 2]).
- Significant or persistent vomiting and/or severe diarrhea. (Note that these gastrointestinal symptoms in isolation do not meet the criteria for anaphylaxis and should be significantly more severe than the typical quickly resolving vomiting that can be a side effect of ICM.)

These criteria should be considered when evaluating and treating an acute ICM reaction in real time and retrospectively when determining the optimal approach to preventing an acute reaction before future contrast-enhanced radiologic studies.

Because most anaphylaxis cases to ICM have been shown to occur within 15 to 30 minutes after administration of contrast, and the mean delay between injection and reaction has been shown to be shorter with higher-grade reactions, the monitoring of routine patients who have received intravenous ICM regardless of a reaction history should fall within this time frame and comply with all federal or state laws or regulations and local, institutional, site, and facility policies, guidelines, or rules.^{26,30}

A serum tryptase value elevated above baseline collected between 30 minutes and several hours (ideally 2 hours but potentially up to 4 to 6 hours) after symptom onset supports a diagnosis of anaphylaxis,³¹ although this laboratory value has no role in acute diagnosis and management. A serum tryptase that is not elevated lacks optimal sensitivity to rule out a diagnosis of anaphylaxis.^{8,32}

Anaphylaxis versus vasovagal reaction.

The vasovagal reaction is an important condition to differentiate from acute anaphylaxis, as detailed in Table 2.³³ Features of

Table 2: Anaphylaxis vs Vasovagal

Presentation	Vasovagal	Anaphylaxis
Onset	Prompt	Within 15-30 min, more serious reactions have more rapid onset
Level of alertness	Lightheaded, transient syncope	May lose consciousness Ranges from alert to persistent loss of consciousness
Respiratory	Slowed, not labored	Dyspnea, cough, rhinorrhea, chest constriction, wheezing, stridor
Skin	Pallor, diaphoresis, clammy	Pruritus, urticaria, or flushing (>90%), angioedema
Gastrointestinal	Nausea, emesis	Nausea, emesis, cramps, diarrhea
Cardiovascular	Hypotension and alertness improve when supine	Hypotension and persistent loss of consciousness
Management	Supine with legs elevated, cold washcloth on face, reassurance, in severe cases intravenous fluids and oxygen may also be needed	Intramuscular epinephrine, supine with legs elevated, intravenous fluid, oxygen, and other measures as warranted

Table 3: Differential Diagnosis to Anaphylaxis

Differential Diagnosis	Distinguishing Features
Exacerbation of asthma	History of asthma
Exacerbation of chronic urticaria	History of chronic urticaria
Inducible laryngeal obstruction or vocal cord dysfunction	No associated cutaneous symptoms
Panic attack	No significant vital sign changes
Munchausen stridor	Factitious anaphylaxis, no significant vital sign changes
Cardiovascular	Chest pain with precordial radiation, diaphoresis, shortness of breath and absence of cutaneous symptoms
Cerebrovascular	Focal neurologic deficit
Flushing syndromes	Preexisting conditions (eg, carcinoid, mastocytosis, pheochromocytoma)
Reaction to other recent medication or food ingestion	Temporal relationship to other medications or foods
Postural tachycardia syndrome	Postural tachycardia without orthostatic hypotension; no associated cutaneous symptoms; history of postural tachycardia syndrome

a vasovagal event may include pallor, weakness, nausea, vomiting, diaphoresis, bradycardia, and hypotension. These reactions can usually be distinguished from anaphylaxis by the absence of skin manifestations: urticaria, angioedema, flush, and pruritus, which are seen in most anaphylaxis cases.³⁴ Patients with vasovagal reactions typically exhibit bradycardia rather than tachycardia generally observed with anaphylaxis,³³ although bradycardia rarely occurs during anaphylaxis owing to a cardioinhibitory reflex. A distinguishing feature is that bradycardia is observed immediately with a vasovagal event whereas in anaphylaxis, tachycardia precedes the onset of bradycardia. Proper recognition of patients with anaphylaxis is important because a delay in administering epinephrine is a risk factor for adverse outcomes.³⁵ It is also important to recognize a vasovagal reaction and treat it appropriately. Patients who are prone to vasovagal reactions are not candidates for premedication before re-exposure to contrast. In addition to vasovagal reactions, there is a differential diagnosis for anaphylaxis that must be considered, as reviewed in Table 3.

Management of anaphylaxis.

The presentation of anaphylaxis is heterogeneous and dynamic, and the treating clinician should continuously reassess the clinical

scenario. Although other therapies such as oxygen and antihistamines may be given as the clinical situation unfolds, the two most important steps in ICM anaphylaxis management are stopping the ICM infusion (if ongoing) and administering epinephrine. There is widespread consensus that epinephrine is the first line of treatment for anaphylaxis.⁸ No absolute contraindications exist for using epinephrine to treat anaphylaxis^{36,37} including patient comorbidities (eg, cardiac disease, age, frailty). Epinephrine counteracts the effects of the myriad of mediators of anaphylaxis and arrests further mediator release. All other therapies, including antihistamines, glucocorticoids, and bronchodilators should be secondarily considered after stabilization. An intramuscular injection of 0.01 mg/kg of a 1:1000 concentration (1 mg/mL) of epinephrine should be administered, with a maximum single dose of 0.5 mg (for >50 kg) which may need to be repeated in severe cases.^{8,38} These doses may be drawn from an ampule via a syringe. Alternatively, epinephrine autoinjectors are available from several manufacturers with prespecified epinephrine doses of 0.3 mg for patients greater than 30 kg and 0.15 mg for children less than 25 to 30 kg.³⁹⁻⁴¹ If staff experience in drawing and administering epinephrine is limited, an autoinjector may minimize errors and expedite epinephrine delivery.^{42,43} It is nonetheless important that staff be adequately trained on autoinjectors (through training devices or simulation) because there

is a risk for accidental finger injection,⁴⁴ although even accidental autoinjection has an overall low risk of permanent morbidity. Epinephrine should be administered into the vastus lateralis in the anterolateral thigh, to allow optimal absorption.^{8,45,46} Intramuscular epinephrine is the first-line therapy for anaphylaxis, but in rare cases of protracted anaphylaxis, intravenous epinephrine infusion (1:10 000 concentration [1 mg/10 mL]) may be necessary.⁸ Delay in administering epinephrine has been associated with anaphylaxis fatalities and increased risk of biphasic reactions,^{8,35,47} but this is not specific to ICM anaphylaxis.

Other treatments should be employed as necessary for anaphylaxis. Fluid resuscitation should commence immediately in patients presenting with hypotension, and patient positioning should be changed to supine or Trendelenburg. Supplemental oxygen may be necessary for patients with respiratory symptoms. H1 and H2 antihistamines are commonly administered in cases of anaphylaxis, but there is only indirect evidence supporting this practice and H1 antihistamines will address only cutaneous manifestations of anaphylaxis, none of which are life-threatening. An attempt at a systematic review of the efficacy of H2 antihistamines in anaphylaxis identify no high-quality evidence supporting this practice.^{8,48} Glucocorticoids have no role in treating acute anaphylaxis given the slow onset of action.⁸ The recent practice parameter update on anaphylaxis also recommended against the administration of glucocorticoids to prevent biphasic anaphylaxis, because multiple studies, including systematic reviews, have not demonstrated clear evidence that glucocorticoids prevent biphasic anaphylaxis.⁴⁹⁻⁵² After suspected anaphylaxis, patients should be kept under observation until signs and symptoms have fully resolved. Because most imaging centers are not staffed or designed for extended observation of patients, any patient suspected of having had anaphylaxis to ICM should be sent to the nearest emergency department.

Patients should be educated regarding the possibility of biphasic anaphylaxis. Biphasic anaphylaxis occurs when the initial symptoms of anaphylaxis resolve completely but then recur up to 72 hours later, with a mean of 11 hours.^{53,54} Protracted anaphylaxis (when anaphylaxis symptoms remain continuous and intravenous epinephrine may be required) occurs even more rarely.⁵⁵ An analysis of 145 patients with ICM anaphylaxis demonstrated that 10.3% developed biphasic anaphylaxis and 4.1% developed refractory anaphylaxis.⁵⁶ Biphasic anaphylaxis is associated with greater severity of the initial reaction and requirement of more than one dose of epinephrine to treat initial symptoms (odds ratio = 4.82; 95% CI: 2.70, 8.58). Evidence suggests that epinephrine administration early in the course of acute anaphylaxis may improve clinical outcomes by reducing the risk of biphasic reaction.⁵⁷⁻⁵⁹

Based on available evidence, it would be prudent to extend observation to up to 6 hours or longer (including hospital admission) for a patient with severe anaphylaxis and/or requiring more aggressive treatment (eg, one or more doses of epinephrine) for potential biphasic event after complete resolution of signs and symptoms.^{8,60} Regardless of severity, all patients should be observed until signs and symptoms of anaphylaxis have fully resolved.

Prevention of Immediate Reactions to ICM

Historical context for corticosteroid prophylaxis.

The initial studies evaluating corticosteroid prophylaxis were done to prevent recurrent immediate reactions with HOCM.⁶¹⁻⁶³

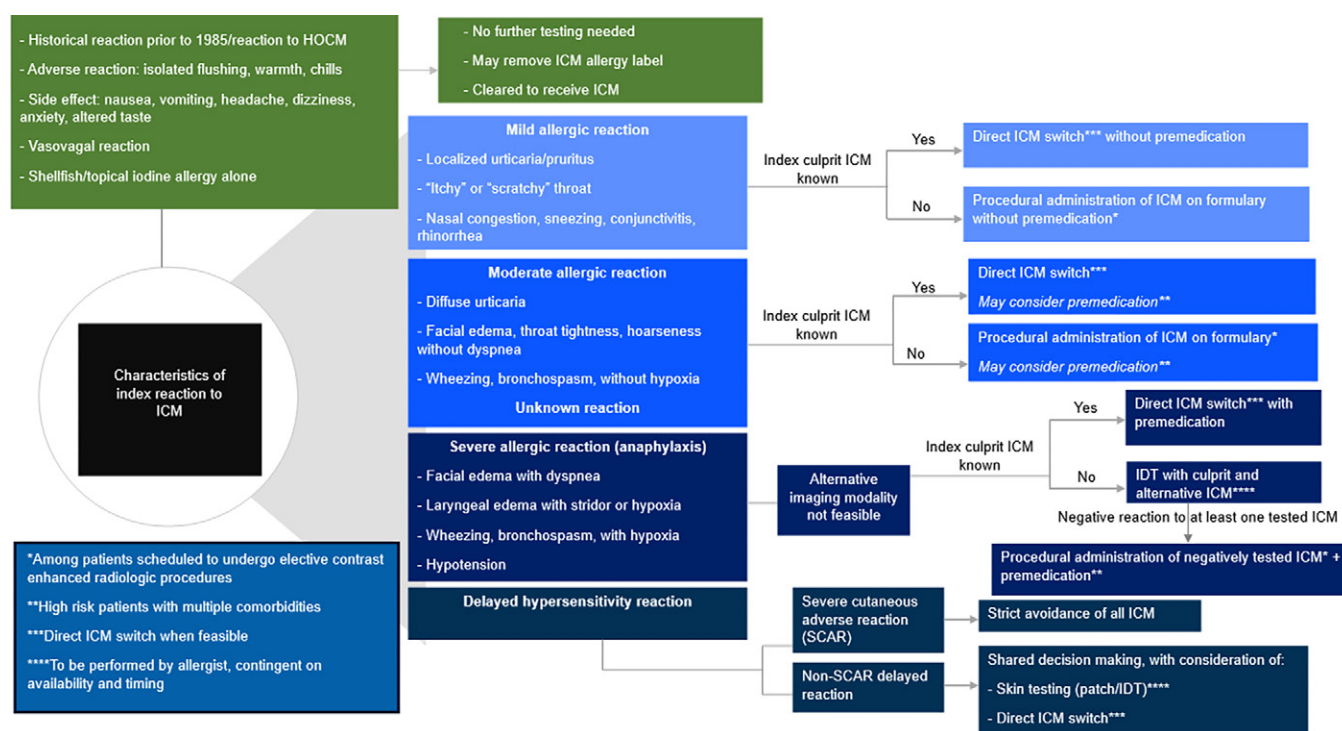
The protocols involved premedication with oral glucocorticoids and H1 antihistamines, with or without H2 antihistamines and ephedrine, to prevent the nonspecific release of histamine and other mediators from circulating basophils, which is the presumed mechanism in most contrast reactions.⁶¹⁻⁶⁴ Studies evaluating the efficacy and safety of premedication entailed substantial variation in medications used and the timing of their corticosteroid administration (eg, prednisone 50 mg 13 hours, 7 hours, and 1 hour before ICM; methylprednisolone 32 mg 12 and 2 hours before ICM).^{61,64-66} Moreover, glucocorticoids take several hours to work.⁶⁷ Glucocorticoid administration is associated with acute basopenia, providing a basis for the efficacy of these premedication regimens.⁶⁸

The risk of adverse immediate ICM reactions has been dramatically reduced with the universal use of LOCM. There is no high-quality evidence supporting the benefit of corticosteroid premedication in preventing recurrent reactions in patients receiving LOCM, owing to variations in premedication protocols and the low rate of severe reactions to LOCM.^{10,17,64,65,69} Despite these unproven and modest benefits, a survey of radiologists in 2009 showed increasing support for using premedication regimens compared with 1995.¹⁰

Is Premedication Recommended for Prior Reactors in Association with the Administration of LOCM?

In making management recommendations, our task force has prioritized the potential for benefit of premedication for severe prior reactors (reduced likelihood of severe immediate reaction) based on very low-quality evidence from HOCM studies being extrapolated to LOCM and very low-quality evidence from LOCM studies, compared with the potential for harm (risk for untoward effects from corticosteroid and antihistamine premedication and burden (diagnostic delay, needing a driver, etc)).

Direct risks of corticosteroid premedication are generally considered to be minor. One of the most studied effects is transient asymptomatic hyperglycemia, generally lasting 48 hours or less.^{70,71} Transient leukocytosis, sleeplessness, mood changes, and potential for increased infection risk have been studied as possible effects of short-term oral corticosteroids, although many reports define short-term as up to 30 days rather than the 12- or 13-hour treatment regimen recommended by the ACR and, until recently, the Joint Task Force on Practice Parameters.^{7,8,65,72-75} Additionally, although considered optional by the ACR, some premedication regimens include diphenhydramine (or other antihistamines, including second-generation ones). Direct risks of diphenhydramine include anticholinergic and sedative effects, which may impair a patient's ability to drive and necessitate coordination with a driver. Indirect risks of premedication include diagnostic delay because of the time required to complete the premedication regimen.⁷⁶ For this reason, the role of premedication has become controversial, with questions raised as to whether the potential benefit (reduction in risk for immediate reaction) outweighs the potential for harm (untoward effects from corticosteroid and antihistamine administration and prolonged length of hospital stay for inpatients).^{77,78} Given the substantially lower rate of immediate reactions with routine use of LOCM, premedication may pose a greater risk for indirect harm than the direct harm this regimen is intended



Flowchart for management of reactions to iodinated contrast media (ICM). HOICM = high-osmolality contrast media; IDT = intradermal testing.

to prevent. Overall, there is limited evidence that premedication for immediate reactions is helpful.⁷⁹

Is Premedication Recommended for Prior Reactors with Moderate and Severe Reactions?

A comprehensive analysis carried out by the Joint Task Force on Practice Parameters⁸ did not demonstrate benefit from premedication to prevent immediate reactions in prior reactors (relative risk = 1.07; 95% CI: 0.67, 1.71) and suggested against routine administration of glucocorticoids and/or antihistamine premedication to prevent immediate reaction before re-exposure to ICM for prior reactors, with a very low certainty of evidence. Considering this, and weighing the potential benefits with the potential for harm or burden with premedication, premedication may still be an option for moderate reactions, but this evidence is of low quality and certainty. We also acknowledge that previous reaction severity may not predict future reaction severity.⁸⁰ We recommend premedication for patients with a history of severe reactions to ICM for whom an alternative imaging study is not an option and when the untoward consequences of premedication and delayed diagnosis are small (Figure),⁷⁸ while acknowledging that the evidence supporting this recommendation is of very low quality. One early landmark trial in LOICM in 1994 was underpowered to evaluate the efficacy of corticosteroids to prevent reactions and included chemotoxic, vasovagal, or other reactions as well as immediate reactions, with decreases seen in physiologic reactions as well as mild to moderate symptoms, but no significant reduction in severe immediate reactions.⁶⁵ A pooled analysis of 736 patients in five retrospective studies included some moderate and severe reactions. Patients who did not receive premedication had initial pooled HSR rates of 0.16 (95% CI: 0.07, 0.35), compared with 0.02 in association with premedication (95% CI: 0.01, 0.06); patients who had prior

HSRs and received premedication were significantly less likely to experience HSRs (odds ratio = 0.09; 95% CI: 0.03, 0.25; $P < .00001$). However, methodologic shortcomings were present in all five studies: (1) There was substantial heterogeneity in corticosteroid and antihistamine premedication regimens across and within these studies; and (2) indications for premedication were not limited solely to moderate or severe reactions. In addition to prior ICM reactions, pretreated patients included those with previous "allergic-like or unknown-type reactions" to ICM, "history of bronchial asthma," or "a history of allergies requiring medical treatment." Although a statistically significant reduction in the rate of moderate or severe reactions was observed compared with no treatment in this recent systematic review and meta-analysis,⁷⁸ these regimens reduce but do not eliminate the risk for an immediate reaction, with breakthrough reactions occurring in approximately 2.1% of this patient group.^{7,69,79,81} Nearly half (48%) of breakthrough reactions may be moderate or severe despite premedication and can be acutely life-threatening or require prompt medical attention.⁸¹ Repeat immediate reactions have been shown to occur in up to 12% of patients with moderate or severe breakthrough reactions and occur more often in patients with moderate or severe index reactions.^{79,81}

When circumstances imply a high risk for serious anaphylaxis based on a history of severe reaction and one or more comorbid conditions (eg, mastocytosis) that imply the greater risk for more serious immediate reaction is present, the balance between the potential for benefit and the potential for harm or burden favors administering premedication with systemic steroids with or without antihistamines. For patients with a history of moderate reaction, a shared decision-making approach, weighing risks versus benefits from an individualized standpoint, allowing the patient to participate in the medical decision-making process by expressing values and preferences, is most appropriate.

Is Premedication Recommended for Prior Reactors with Mild Reactions?

Based on the evidence for benefit compared with the potential for harm or burden, premedication is not recommended for patients with a history of mild reaction (Figure). As is the case with the previous recommendation for moderate to severe prior reactors, additional studies that are methodologically sound are required to determine whether the benefit from premedication before administration of LOCM for prior reactors exceeds the harm or burden associated with this treatment. Given the low confidence in the certainty of evidence, future studies may lead to a change in this recommendation. Although premedication is not generally recommended in this patient group, we acknowledge that such patients may be premedicated in rare instances after shared medical decision-making between the patient and the health care provider or because of strong patient preferences or clinical circumstances.

Should Direct Switching from Incriminated ICM to an Alternative Agent Be Performed?

A direct switch away from the incriminated ICM agent may protect against a repeat breakthrough reaction and may also be more effective than premedication. Abe et al⁸² reported that a direct switch to an alternative agent was associated with greater protection against recurrent HSR compared with steroid premedication. However, most patients had a mild reaction without a standardized switching protocol. The overall breakthrough reaction rate was 28% when the same ICM was administered without steroid premedication compared with 17% when the same ICM was given with steroid premedication and an 8% recurrence rate with a direct switch between LOCM and no premedication. Concordantly, a multicenter study reviewed the incidence of breakthrough reactions among patients with re-exposure to ICM and a history of moderate to severe HSR.⁸³ This study similarly noted that directly changing from the culprit agent to an alternative ICM led to a significantly decreased breakthrough rate of 13.4% compared with 27.6% when the same ICM was used.

The most substantive evidence thus far comes from a study by McDonald et al.⁸⁰ The authors performed a retrospective evaluation of 1973 patients with immediate ICM-induced HSR who underwent 4360 contrast-enhanced CT scans and compared outcomes with steroid prophylaxis versus direct ICM switch. Premedication alone was not effective at preventing breakthrough reactions in patients who received the same ICM agent as the index reaction: 26% (44 of 172) versus 25% without prophylaxis (73 of 298). However, the direct ICM switch was highly effective at preventing breakthrough reactions and resulted in breakthrough reactions in 3% of patients with premedication and 6% without premedication.

Most recently, a systematic review and meta-analysis of six studies, including 7155 adult patients with prior ICM-induced HSR, compared outcomes in 2826 patients who received the same ICM and 4329 who received a different ICM agent.⁸⁴ The studies were widely heterogeneous with no standardization in either the switching methods or the premedication regimen used, which limits the interpretation of these data. Substitution with an alternative ICM agent decreased the risk of breakthrough reactions by 61% compared with using the same agent in patients

with prior immediate HSRs. These data must be interpreted with caution given the observational nature of the studies and limited quality, but they provide support for changing the culprit ICM agent if possible. Severe reactions occurred in about 0.2% of patients ($n = 11$ of 7155 patients in the six studies reporting reaction severity), limiting the ability to interpret the effect on severe reactions. A subanalysis in this meta-analysis suggested that premedication did not decrease the risk of recurrent reactions in the aggregate cohort.⁸⁴ The strategy of a direct switch is supported by the finding that patients with a positive skin test to the index ICM often test negative to alternative agents.^{28,85-87} Overall, the data favor switching ICM agents to decrease recurrent reactions in situations where this is possible and the index agent is known (Figure). There is no known direct harm to the patient from switching agents.

The ACR Manual on Contrast Media advises a direct switch to an alternative LOCM in patients with a history of immediate reaction to ICM when the inciting agent is known, whereas the 2020 Practice Parameter on Anaphylaxis did not discuss this potential strategy. The task force found the data on switching agents compelling enough at this time to recommend it for all levels of severity of index reactions when feasible. This caveat, “when feasible,” is in place for several reasons including the absence of a documented culprit ICM in the EHR and the lack of patient knowledge regarding which agent to replace. One study showed that only 1.6% of patients were able to name the contrast agent to which they reacted.⁸⁸ Additionally, the task force recognizes from practical experience that switching agents may be logistically challenging or even impossible depending on institutional limitations, as highlighted by the recent ICM severe contrast shortage. In the United States, ICM is supplied by only four companies, two of whom supply 90% of the ICM infusions. This, coupled with the limited distribution channels for ICM and consolidation of buyers into group purchasing organizations, results in many institutions having preferred vendor contracts, which limits the number of alternative contrast agents allowed on formulary and may be cost-prohibitive because certain agents may be significantly more expensive.⁸⁹ In addition, it may be workflow-prohibitive to switch agents using multiple-dose injectors, some of which are approved by the Food and Drug Administration for single-vendor contrast agents and could result in large amounts of wasted contrast from needing to switch agents before using up a multiple-dose vial.

Delayed Reactions

Epidemiology of Delayed Reactions

The incidence of delayed HSRs is difficult to quantify accurately owing to the delayed onset of presentation (anywhere from hours up to 1 week after ICM administration), the difficulty of establishing causality, and missed reporting. Reactions may also not be characterized according to commonly used grading schema, creating a barrier to optimal characterization.^{18,83} The available literature does not always distinguish between immediate and delayed reactions. Each of these complicating factors could result in either underestimation or overestimation of the true incidence of this condition.⁹⁰

Noting these limitations, delayed HSRs are thought to be less common than acute HSRs, comprising an estimated 0.5% to 23% of all ICM HSRs.⁹¹ Several retrospective studies and at least one

prospective study suggest a prevalence of 0.5% to 46%, although the inclusion of physiologic-type reactions (eg, altered taste sensation or restlessness) and inclusion of both intra-arterial and intravenous administration of ICM may have contributed to the wide range.⁹²⁻⁹⁶

Pathophysiology of Delayed Reactions

Delayed HSRs could be related to a T cell–mediated mechanism, with skin biopsies demonstrating a perivascular infiltration of CD4 and CD8 T cells.^{15,97} Evidence after allergy investigations, such as ST and drug challenge, implicates an immunologic mechanism in more than 50% of reported HSRs.^{22,98-100}

It is suspected that the immunologic mechanism of these delayed reactions is attributed to the structure of the ICM, because nonionic dimeric ICM (eg, iodixanol) is associated with more cutaneous reactions compared with nonionic monomeric ICM, although the exact mechanism for nonallergic urticaria and/or angioedema more than 6 hours after ICM administration is unknown.⁷

Identifying Delayed Reactions to ICM

A retrospective review of more than 74 000 adverse reactions to intravenous LOCM injections throughout Korea suggested that DHRs comprised 11.4% of all contrast reactions; greater than 99% manifested with solely cutaneous symptoms, and 88% in the form of a maculopapular exanthem.⁹³

Whereas the vast majority of DHRs would be classified as mild according to the schema described by the ACR,⁷ there are case reports of severe cutaneous adverse reactions (SCARs) such as acute generalized exanthematous pustulosis,¹⁰¹⁻¹⁰⁴ drug reaction with eosinophilia and systemic symptoms,⁹⁷ and Stevens-Johnson syndrome/toxic epidermal necrolysis.¹⁰⁵⁻¹⁰⁹ There is no role for extending monitoring patients with a history of a delayed reaction at the time of a subsequent contrast study beyond routine monitoring.

Prevention of Delayed Reactions

Should premedication and/or direct switch be used in patients with a history of delayed reaction to ICM?

Currently, the literature is limited regarding the rate of subsequent reactions after an initial delayed reaction to ICM, the risk factors for or the underlying mechanisms of these subsequent reactions, and the accuracy of allergy testing. The available evidence does not support premedication as a strategy to prevent recurrent reactions. Only a small retrospective study showed a possible benefit for steroid use before and after intervention in nonsevere delayed reactions.¹¹⁰ Cross-reactivity among the different ICM agents has been described for both immediate and delayed reactions.⁸⁵ A higher rate of cross-reactivity has been described in patients with delayed reactions compared with patients with immediate reactions.¹¹¹ To date, no formal evidence-based recommendations can be formulated concerning direct switching for patients reporting non-SCAR delayed reactions. The final decision about direct switching in this patient population should be made by the patient and treating physician and depends on the indication for the study.

Summary for Delayed Reactions

For patients with a history of delayed reactions to ICM, there is no evidence to support premedication as a strategy to prevent recurrent reactions. Patients with a SCAR to ICM should strictly

avoid ICM in the future.^{112,113} For patients with a non-SCAR reaction, the decision to use contrast and whether to direct switch should be made by the patient and treating physician depending on the need of the study and the reaction history.

Iodinated Contrast Media Myths

Is Allergy a Risk Factor for Immediate or Delayed ICM Reactions?

In 1975, a prospective study of factors associated with adverse reaction to HOCM in 112 003 patients described an association of allergy with a greater rate of adverse reaction from contrast infusion.¹¹⁴ An elevated rate of adverse reactions to HOCM was associated with self-reported allergy to medications and foods, such that the authors concluded “the overall incidence of adverse reactions in patients with allergy is about twice that in the general population.”¹¹⁴

This study had several methodologic weaknesses: (1) The data were obtained via a questionnaire with no corroborative testing performed to confirm the self-reported history of allergy to drugs or foods; (2) there was no evaluation to verify the self-described history of asthma, allergic rhinitis, or general allergy; and (3) patients who experienced a reaction from HOCM consistent with anaphylaxis or symptoms related to the effects of mast cell mediator release were not distinguished from those who experienced vasovagal, hemodynamic, or other adverse reactions.

Is Seafood Allergy Associated with an Elevated Risk for Anaphylaxis for ICM and an Indication for Premedication Before Contrast Exposure?

Survey data from 2008 demonstrated that most radiology and cardiology participants screen for seafood allergy before the administration of ICM, and a significant subset would either withhold ICM or administer premedication for patients responding affirmatively.¹¹⁵ The task force believes that the surveillance study by Shehadi¹¹⁴ is likely the original source for the mistaken belief that seafood allergy is associated with greater risk from contrast infusion.

Self-reported allergy to other foods was also more common in individuals who had contrast media reactions; however, the highest reaction rate (14.98%) was found among those with allergy to seafood or shellfish. A clear association between seafood allergy and greater risk for immediate ICM reactions has not been established. Patients with self-reported seafood allergy and those with confirmed IgE-mediated (allergic or anaphylactic) potential to crustaceans are not at elevated risk for immediate or delayed ICM reaction compared with the general population, and thus should not be regarded as candidates for risk reduction measures.¹¹⁶

Is Iodine Allergy Associated with an Elevated Risk for Anaphylaxis from ICM and an Indication for Premedication Before Contrast Exposure?

It is unclear how seafood allergy and iodine allergy became linked.¹¹⁷ As older contrast agents dissociated into ions containing an iodinated benzene ring, they were regarded as iodine-based. When the myth developed that seafood allergy was related to contrast reactions,¹¹⁴ it is possible that a causal link between the iodine content of crustaceans and contrast material was assumed. However, the mechanism for immediate ICM reaction is most likely related to the physiochemical properties

of these media and is unrelated to its iodine content.³³ IgE-mediated reaction to crustaceans is unrelated to iodine, but rather to tropomyosin.¹¹⁸

Iodine is not an allergen. As a public health intervention, iodine was added to table salt to prevent iodine deficiency, such that the population is universally exposed to iodine. There is no evidence to support the assertion that patients who have been labeled as having iodine allergy are at elevated risk for a contrast media reaction.¹¹⁹ Patients who have had (1) iodide-induced sialadenitis or (2) an adverse reaction to potassium iodide are also not candidates for premedication before ICM administration.^{120,121}

Is a Prior Gadolinium-based Contrast Media Immediate Reaction an Indication for Premedication Before Contrast Exposure?

A few studies demonstrated an increased risk for immediate reaction to ICM in patients with a history of immediate reaction to gadolinium-based contrast media (GBCM); however, these were self-reported adverse reactions, and some (eg, headache, dizziness, or injection site reaction) were not immune-mediated.^{122,123} In addition, it is unclear whether patients who have had non-IgE mediated anaphylaxis from GBCM are at elevated risk from receiving ICM based on an indirect hazard associated with shared risk factors. From a pharmacologic standpoint, there is no similarity between the chemical structures of ICM and GBCM to suggest cross-reactivity. Adverse reactions to GBCM occur at a lower rate than to ICM. The reported rate of anaphylaxis ranges from 0.004% to 0.7%; severe reactions occur in the range of 0.001% to 0.01%.^{7,124}

There is currently no clear evidence to support premedication for ICM owing to a history of immediate reaction to GBCM.

Skin Testing and Rapid Drug Desensitization

Should ST to ICM Be Performed for a History of Immediate Reactions?

The current European guidelines recommend ST with the culprit agent and a panel of alternative contrast media for patients with a history of ICM-induced anaphylaxis, to identify a tolerated agent.¹⁵ Skin testing may be helpful in the evaluation of higher-risk patients with a history of severe HSRs, especially in those with a history of reaction in the past 6 months who need repeat contrast administration.¹²⁵⁻¹²⁷ However, ST to ICM is not routinely performed in the United States, and access to ST in a timely manner may limit routine implementation.¹²⁸

It is recommended to perform skin prick testing and intradermal testing (IDT) with undiluted ICMs and 1:10 diluted ICM solution (300-320 mg/mL), respectively.^{15,26,129-131} Intradermal testing results may lack optimal specificity owing to an irritant effect; conversely, a negative skin test does not preclude a recurrent reaction.¹²⁶ The lack of standardized ST methodology and protocols in the literature to date also complicates the comparison of results across the literature and conclusions regarding its diagnostic accuracy. Overall, ST to ICM has a negative predictive value of 80% to 97.3% for immediate reactions; however, the positive and negative likelihood ratios of ICM ST have not been determined.^{15,132} Reaction severity appears to correlate with ST positivity,¹²⁵ and in one study, 81.8% of patients with ICM-induced anaphylactic shock had positive ST results with ICM, with largely negative results in mild reactors.²⁶ This was reproduced in a meta-analysis of patients

with ICM-induced immediate HSR, in which pooled per-patient ST positivity rates increased from 17% (95% CI: 10%, 26%) in an unselected population to 52% (95% CI: 31%, 72%) among patients with severe index reactions.¹²⁷ The timing of the investigation is also important; ST within 6 months of the reaction is recommended owing to higher sensitivity.¹⁵

Allergist referral for ST in the setting of severe HSRs may be helpful, particularly if the culprit agent is unknown, for the selection of a potentially tolerated agent and for a direct switch to an alternative agent if the ICM used during the index reaction is known. However, a risk-benefit discussion with the patient is important because 7% of patients with negative testing react to contrast on repeat administration, and the benefit of ST needs to be clarified through prospective studies.^{133,134} Studies investigating the role of ST in the evaluation of immediate HSRs are listed in Table 4. The Figure outlines a suggested workflow.

Should ST to ICM Be Performed for Patients with a History of Delayed Reaction?

Although ST has been evaluated in delayed ICM reactions, its accuracy is poorly understood.^{87,137-139} Skin test modalities include patch testing and delayed IDT with the culprit and alternative ICM.^{15,22,90,98,126,137,140,141} The described nonirritant concentration for IDT and patch testing is 1:10 and undiluted, with reading performed at 24 to 72 hours.^{15,90,137,142,143} The specificity of delayed IDT had been calculated at 100%,^{86,127,138} but the sensitivity is unknown at this time.¹²⁷ A recent meta-analysis demonstrated that in vivo investigations were positive in 16.9% to 53.5% of patients, with positive provocation after ST in 0% to 34.6% of them.^{98,131} The negative predictive value of a negative skin test and challenge has been calculated at 90% to 96% in some clinical studies.^{85,87,98,144} In another meta-analysis looking at patients with positive skin tests, alternative ICMs were tolerated in 71% (75 of 105).⁹⁸

To date, no formal evidence-based recommendations can be formulated concerning the validity of performing ST for patients reporting non-SCAR delayed reactions. The final decision about ST in this patient population should be made by the patient and treating physician and depends on the need of the study.

Should ST Be Used as a Prescreening Tool in Patients Without a Reaction History?

Empirical IDT of unselected patients has been shown to have extremely low sensitivity and minimal positive predictive value (both ~0%) and is not predictive of future HSRs.¹³¹ Prescreening is therefore not recommended.

Is There a Role for Rapid Drug Desensitization?

Rapid drug desensitization is a procedure used to induce temporary drug tolerance in patients with prior immediate HSR when there are no ideal treatment alternatives. Rapid drug desensitization temporarily modifies the hypersensitivity response to a medication through the administration of gradually incremental drug doses.

Rapid drug desensitization protocols for ICM allergy have been successfully undertaken in patients with a history of breakthrough anaphylaxis despite premedication to enable coronary angiography.¹⁴⁵⁻¹⁴⁹ Steroid or antihistamine premedication was used in all published rapid drug desensitization protocols, which can be found in the cited literature and is beyond the scope of this report.

Unmet Needs Requiring Future Research

First and foremost, there is a need to document in the EHR (1) the inciting agent for the contrast reaction, and (2) a description of the type of contrast reaction and treatments received. To standardize for future large-scale studies, the radiology community should use a standard lexicon for symptom descriptors and phenotypes such as adopting those used in the allergy and immunology literature.¹⁵⁰ There continues to be a need to identify those at increased risk for ICM reactions and to establish the utility of risk reduction measures including whether premedication with antihistamines and corticosteroids confers benefits that outweigh the potential for harm or burden, and the value of switching agents. In making this recommendation, we recognize this will require large, methodologically sound multicenter research studies and/or the establishment of a national registry. Because of the rarity of moderate and severe reactions, it may be challenging to perform a large multi-institutional prospective randomized study to achieve the overall number of injections required for statistical significance. Therefore, a national registry may be a more practical solution to acquire similar data retrospectively. Further efforts are needed to incorporate tryptase measurements after a severe ICM reaction in risk stratification for future ICM-enhanced studies. There is also a need to investigate further the value and potential role that ST can have in identifying alternative tolerable ICM agents and the feasibility and impact on the health care system.

Summary Statements

This document contains joint consensus statements endorsed by the ACR and the AAAAI, which are intended to improve and standardize the care of patients who experience or have a history of an adverse reaction to ICM. These consensus recommendations are based on the best evidence and apply only to intravenous administration of ICM. High-quality evidence and methodologically rigorous studies are lacking owing to (1) the rarity of moderate and severe reactions to low-osmolality iodinated contrast agents; (2) the paucity of methodologically sound studies; and (3) the heterogeneity of published studies, including the multiplicity of premedication and ST regimens, variations in patient selection for premedication, and differing contrast agents used in switching methodology. These recommendations should not be taken as definitive standards of practice; they may be subject to change once additional and more definitive evidence becomes available. Given these limitations, the strength of recommendation is limited for any of the recommendations with limited strength of evidence unless otherwise specified subsequently. The study quality and strength of evidence were determined according to the ACR Appropriateness Criteria Evidence Document. (A concise summary and adaption of the process and the recommendations with associated strength of evidence references can be found in Appendices A, B, and C of the document).¹¹

Table 4: Summary of Evidence for Skin Testing in Evaluation of Iodinated Contrast Media Allergy

Study	Study Design	Clinical End Point	Study Groups	Skin Test Protocol	DPT Protocol	Skin Test Results	DPT Results	Conclusion
Ahn et al (2022) ¹³⁵	Retrospective cohort study	Compared two DPT doses for challenge with ST-negative ICM. Examined rate of breakthrough reactions (BTR) in ST and challenge-negative patients during CT scans after steroid premedication	Korean cohort (n = 85) with history of ICM-induced anaphylaxis	IDT (1:10) with task force of ICM	IV challenge using two DPT doses (10 vs 30 mL)	ST sensitivity 74%	9.6% ST-negative patients had positive DPTs (3.6%)/BTRs (7.6%)	80% of BTRs were severe with 10-mL DPT dose. No severe reactions with 30-mL DPT dose, which may suffice to rule out BTRs
Gamboa et al (2021) ¹²⁵	Prospective cohort study	Examined cross-reactivity between iomeprol and iopamidol among patients with iomeprol-induced immediate HSR and tolerance to alternative agents	Spanish cohort (n = 216) with history of ICM-induced immediate HSR	IDT (1:10) with task force of ICM	IV challenge with 100-mL dose (no premedication)	ST sensitivity 20.4% (32 of 36 selective ST-positive iomeprol)	84.7% ST-negative patients with iomeprol-induced reactions tolerated IV challenge	Iomeprol-allergic patients had uneventful CT scans with alternative ICM (no premedication)

(Table 4 continues)

Table 4 (continued): Summary of Evidence for Skin Testing in Evaluation of Iodinated Contrast Media Allergy

Study	Study Design	Clinical End Point	Study Groups	Skin Test Protocol	DPT Protocol	Skin Test Results	DPT Results	Conclusion
Kwon et al (2019) ¹³⁴	Retrospective cohort study	Evaluated IDT to ICM in patients with index reaction to a known causative agent Examined the rate of BTRs in patients during CT scans after premedication, grouped by IDT results to the index culprit ICM	Korean cohort (n = 69) with history of immediate HSR to known culprit ICM	IDT (1:10) with task force of ICM	N/A	38 patients with positive IDT to culprit ICM (CUL-PRIT+) 31 patients with negative IDT to culprit ICM (CUL-PRIT-) ST sensitivity 87%	N/A	16 CULPRIT+ and 22 CULPRIT- patients had ICM re-exposure CULPRIT+ group: four of five patients had BTRs with IDT-positive alternative ICM, no BTRs with IDT-negative ICM CULPRIT- group: no BTRs with IDT-positive alternative ICM, two BTRs with IDT-negative alternative ICM ST useful in selecting safe alternative only with positive IDT to culprit ICM
Trautmann et al (2019) ¹²⁶	Retrospective cohort study	Assessed the NPV of ST for ICM	German cohort (n = 45), 32 with history of immediate HSR	IDT (1:10) to battery of ICM	IV challenge with 49-mL total dosed at 30-min increments	ST-positive patients (11) categorized as allergic; ST-negative patients (21) categorized as nonallergic All ST-positive patients had moderate to severe anaphylaxis; ST-negative patients had only urticaria	Of 10 allergic patients, all tolerated IV challenge with ST-negative alternative RCM	IDT highly sensitive in identifying allergic patients DPT with ST negative ICM is safe and helps to identify a tolerated alternative ICM

(Table 4 continues)

Table 4 (continued): Summary of Evidence for Skin Testing in Evaluation of Iodinated Contrast Media Allergy

Study	Study Design	Clinical End Point	Study Groups	Skin Test Protocol	DPT Protocol	Skin Test Results	DPT Results	Conclusion
Clement et al (2018) ²⁶	Prospective multi-center cohort study	Investigated frequency of immediate ICM-induced HSR Correlation of positive ST with likelihood of true ICM-induced allergic reactions	French cohort (n = 209) with history of immediate HSR	IDT (1:10 and full-strength) to battery of ICM	N/A	41 (19.6%) positive ST results to ICM	N/A	Positive ST correlated with clinical severity, cardiovascular signs, and histamine and tryptase concentrations
Schrijvers et al (2018) ⁸⁵	Retrospective cohort study	Assessed the NPV of ST for ICM in predicting reactions during future ICM re-exposure with variable premedication use	French cohort (n = 597), 423 (70.9%) with history of immediate HSR	IDT (1:10) to battery of ICM	N/A	Positive ST: 56 of 423 patients NPV of ST: 94.2%	N/A	172 (40.6%) re-exposed to ICM with BTRs in 10 of cases (5.8%) 16 of 17 ST-positive patients (94.1%) tolerated re-exposure without a reaction 201 of 216 ST-negative patients (93.1%) tolerated re-exposure
Lerondeau et al (2016) ¹¹¹	Retrospective cohort study	To analyze ICM cross-reactivity in immediate and delayed HSR based on ST and DPT	n = 38 with history of immediate HSR	IDT (1:10) to battery of ICM	IV challenge with 1/100 to >1/10 final dose	24 (63.1%) ST-positive	Two (5.2%) positive challenges	High rate of cross-reactivity (67%) for immediate and delayed reactions based on ST
Yoon et al (2015) ¹²⁷	Meta-analysis	Evaluated the diagnostic potential of ST in patients with ICM-induced immediate HSR in predicting tolerance to ST-negative agents	Meta-analysis of 21 studies investigating ST to ICM	SPT (full strength) and IDT (1:10) with task force of ICM	N/A	ST-positive rate 17% in immediate HSR and 52% with severe immediate HSR	N/A	7% BTR rate to ST-negative ICM

(Table 4 continues)

All imaging centers should be prepared to manage an adverse contrast reaction related to the administration of intravenous contrast material in any patient regardless of a history of adverse reaction and should include personnel, equipment, and supplies to treat anaphylaxis. Although specific details are outside the scope of this document, suggested supplies, equipment, and on-site personnel can be found in the ACR Contrast Manual and Statement from the Drugs

and Contrast Media Committee on Supervision of Contrast Material Administration.¹⁵¹

Recommendations

Documentation

1. The occurrence of an ICM HSR and manifesting symptoms should be documented in the allergy field or module of the EHR

Table 4 (continued): Summary of Evidence for Skin Testing in Evaluation of Iodinated Contrast Media Allergy

Study	Study Design	Clinical End Point	Study Groups	Skin Test Protocol	DPT Protocol	Skin Test Results	DPT Results	Conclusion
Prieto-Garcia (2013) ¹³⁶	Retrospective cohort study	Evaluated the predictive value of IDT in patients with index reaction to a known causative agent Evaluated outcomes with controlled challenge testing using alternative ST-negative ICM in ST-positive ICM reactors	Spanish cohort (n = 106) with history of ICM-induced immediate HSR	IDT (1:10) to battery of ICM	IV challenge with 120-mL dose (no pre-medication)	IDT-positive to culprit ICM in 11 of 106 patients (10.4%)	Five of 11 patients tolerated DPT with ST-alternative ICM Two additional patients tolerated ST-alternative ICM during subsequent CT	Patients with + IDT to culprit ICM tolerated subsequent exposure to ST-alternative ICM without premedication
Caimmi et al (2010) ⁸⁷	Retrospective cohort study	To evaluate the NPV of ICM skin tests	French cohort (n = 24) with history of ST for ICM-induced immediate HSR and subsequent re-exposure to ICM (no premedication)	SPT (full strength) and IDT (1:10) with task force of ICM	N/A	ST positive in 17 of 24 patients	N/A	High NPV of ST ~96% in preventing BTRs following re-exposure to ICM
Brockow (2009) ²²	Prospective cohort study	To evaluate the sensitivity and specificity of ICM ST in previous reactors	European cohort (n = 122) with history of ICM-induced immediate HSR	SPT (full strength) and IDT (1:10) with task force of ICM	N/A	ICM ST had 96% to 100% specificity	N/A	~50% immediate reactors were ST+ on tests performed 2 to 6 months of the index reaction

BTR = breakthrough reaction, CT = computed tomography, DPT = drug provocation test, HSR = hypersensitivity reaction, ICM = iodinated contrast media, IDT = intradermal testing, IV = intravenous, N/A, not available, NPV = negative predictive value, ST = skin testing.

by the treating health care professional. This should include the specific inciting agent and avoid the general term *iodinated contrast agent* and the term *iodine* to optimize future ICM reaction management. Furthermore, inaccurate or incomplete historical ICM reactions should be updated in this section of the EHR when additional information becomes available. Documenting the reaction in the radiology report could also be considered, but only in addition to the allergy field or module in the EHR.

Strength of evidence: Limited

Strength of recommendation: Strong

This is a strong recommendation despite limited strength of evidence, because it is expert consensus that it is necessary

to document the index HSR and inciting agent accurately to be able to optimize future management for the patient who returns for a contrast-enhanced CT and to be able to provide optimal management as additional evidence becomes available. This will also aid in research into best practices.

Premedication (Glucocorticosteroids with or without Antihistamines)

2. For patients with a history of **mild** immediate ICM HSRs, **premedication is not recommended.**

Strength of evidence: Limited

Strength of recommendation: Limited

3. For patients with a history of **mild** immediate ICM HSRs, **switching the contrast agent is recommended** when feasible (eg, dependent on knowing the inciting agent[s], availability of an alternative agent, and institutional constraints).

Strength of evidence: Limited

Strength of recommendation: Limited

4. For patients with a history of **moderate** immediate ICM HSRs, **switching the contrast agent is recommended** when feasible (eg, dependent on knowing the inciting agent[s], availability of an alternative agent, and institutional constraints).

Strength of evidence: Limited

Strength of recommendation: Limited

5. For patients with a history of **moderate** immediate ICM HSRs, **premedication may be considered**.

Strength of evidence: Limited

Strength of recommendation: Limited

6. For patients with a history of **severe** immediate ICM HSRs, it is **recommended** first to consider **alternative studies** (eg, contrast-enhanced magnetic resonance imaging, ultrasound, contrast-enhanced ultrasound, non-contrast CT).

Strength of evidence: Expert consensus

7. For patients with a history of **severe** immediate ICM HSRs, when there is no acceptable alternative study, **switching the contrast agent is recommended** when feasible (eg, dependent on knowing the inciting agent(s), availability of an alternative agent, and institutional constraints).

Strength of evidence: Limited

Strength of recommendation: Limited

8. For patients with a history of **severe** immediate ICM HSRs, when there is no acceptable alternative study, **premedication is recommended**.

Strength of evidence: Limited

Strength of recommendation: Limited

9. For patients with a history of **severe** immediate ICM HSRs, the study should be performed in a hospital setting with a rapid response team available including personnel, equipment, and supplies to treat anaphylaxis regardless of whether the patient underwent agent switching or premedication.

Strength of evidence: Expert consensus

10. Premedication is **not recommended** for only an isolated history of HSR to HOCM or allergy to an unknown iodinated contrast agent before Food and Drug Administration approval of the first low-osmolality agent in 1985.

Strength of evidence: Limited

Strength of recommendation: Limited

11. Premedication is **not recommended** for only an isolated history of delayed ICM HSR.

Strength of evidence: Expert consensus

12. Premedication is **not recommended** for only an isolated history of HSR to gadolinium-based contrast agents when the patient is to receive ICM.

Strength of evidence: Limited

Strength of recommendation: Limited

13. Premedication is **not recommended** for only an isolated history of shellfish or iodine allergy, including topical povidone-iodine allergy.

Strength of evidence: Limited

Strength of recommendation: Strong

No clear association between shellfish allergy and an increased risk of ICM hypersensitivity has been found in clinical studies or via pathogenesis. Iodine is an essential element in thyroid function and is not an allergen. See section on ICM Myths for detailed rationale.

14. Premedication is **not recommended** for only an isolated history of asthma.

Strength of evidence: Expert consensus

15. Premedication is **not recommended** for any of the following in isolation: drug allergy, food allergy, stinging insect allergy, family history of ICM HSR, female sex, asthma, use of beta-blockers or ACE inhibitors, or a history of cardiovascular disease.

Strength of evidence: Expert consensus

16. Premedication is not recommended for non-immune mediated adverse reaction or intolerances characterized as "physiologic reactions" in the ACR Manual.

Strength of evidence: Expert consensus

Anaphylaxis and Its Treatment

17. Anaphylaxis to ICM should be considered when the acute onset of illness occurs within minutes after intravenous ICM administration and in the absence of other known allergens or triggers. In such situations, anaphylaxis is considered likely if any two or more of the following criteria are met:

a. Involvement of skin/mucosal tissue or both

b. Respiratory compromise

c. Reduced blood pressure or associated symptoms of end-organ dysfunction (Severe hypotension may preclude the manifestation of any other anaphylaxis symptoms and anaphylaxis should be considered when there is no other source for the acute onset of severe hypotension within minutes of intravenous ICM administration such as shock, sepsis, or vasovagal reaction.)

d. Significant or persistent vomiting and/or severe diarrhea (These gastrointestinal symptoms in isolation do not meet criteria for anaphylaxis and should be significantly more severe than the typical quickly resolving vomiting that can be a side effect of ICM.)

Strength of evidence: Limited

Strength of recommendation: Strong

This is the accepted definition of anaphylaxis.

18. Epinephrine is recommended as the first-line treatment for anaphylaxis.

Strength of evidence: Limited

Strength of recommendation: Strong

This is a strong recommendation from the Practice Parameters on Anaphylaxis from the AAAAI and the American College of Allergy, Asthma and Immunology. Epinephrine is the treatment of choice based on the mechanism of action and data demonstrating adverse outcomes when epinephrine is not given or there is a delay in administration.

19. H1 antihistamines should not be administered as the primary and only treatment for anaphylaxis.

Strength of evidence: Limited

Strength of recommendation: Strong

This is a strong recommendation from the Practice Parameters on Anaphylaxis from the AAAAI and the American College

of Allergy, Asthma and Immunology. H1 antihistamines should be used primarily for reactions limited to the skin.

Follow-up in Severe Immediate ICM HSR

20. After a severe immediate ICM HSR, when feasible, it is recommended that a serum tryptase level is drawn ideally within 2 hours but potentially up to 4 to 6 hours and compared with baseline or recovery level drawn more than 24 hours after all signs and symptoms have resolved to support the diagnosis of anaphylaxis.

Strength of evidence: Limited

Strength of recommendation: Limited

21. After a severe immediate ICM HSR, it is recommended that the radiologist consider referral to a board-certified allergist for further evaluation and consideration of ST to identify alternative ICM agents that can be tolerated for future nonurgent examinations. For higher sensitivity, the testing should be performed within 6 months of the reaction.

Strength of evidence: Limited

Strength of recommendation: Limited

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