

CAR/CSACI Practice Guidance for Contrast Media Hypersensitivity

Adam Byrne^{1,2}, D. Blair Macdonald^{3,4}, Iain D. C. Kirkpatrick^{5,6}, Magali Pham^{7,8}, Courtney R. Green⁹, Ana Maria Copaescu¹⁰, Matthew D. F. McInnes^{4,11}, Ling Ling¹², Anne Ellis¹³, and Andreu F. Costa^{14,15}

Canadian Association of Radiologists Journal
1–17

© The Author(s) 2025



Article reuse guidelines:

sagepub.com/journals-permissions

DOI: 10.1177/08465371241311253

journals.sagepub.com/home/caj



Abstract

Contrast media, including iodinated contrast media and gadolinium-based contrast agents, are commonly administered pharmaceuticals with excellent safety profiles. However, a minority of the population may experience a hypersensitivity reaction following intravenous administration. Hypersensitivity reactions can be immediate or delayed, and range from mild, such as urticaria, to severe, including anaphylaxis. There is emerging evidence that longstanding pretreatment protocols, such as diphenhydramine and corticosteroids, are ineffective and have the potential for side effects and other harms. Moreover, the evidence for efficacy on which this practice is based is weak and outdated. A joint collaborative working group of representatives from the Canadian Association of Radiologists and the Canadian Society of Allergy and Clinical Immunology was assembled to inform medical professionals and hospital policies regarding hypersensitivity reactions to contrast media. The objectives of the working group were to provide an overview of the epidemiology, physiology, risk factors, and types of hypersensitivity reactions; to synthesize the evidence for pretreatment strategies that minimize the risk of a breakthrough reaction for both iodinated contrast media and gadolinium-based contrast agents; to review the allergy investigations used to evaluate patients with a history of severe hypersensitivity reaction; and to provide an overview of existing guidelines. Following appraisal of the evidence, the working group established recommendations based on consensus in this practice guidance.

Résumé

Les produits de contraste, notamment les produits de contraste à base d'iode et les agents à base de gadolinium, sont fréquemment administrés et présentent d'excellents profils de sécurité. Toutefois, une petite partie de la population peut présenter des réactions d'hypersensibilité à la suite d'une administration par voie intraveineuse. Les réactions d'hypersensibilité ont lieu immédiatement ou quelque temps après l'administration, et leur sévérité peut être faible, comme dans le cas d'une

¹ Department of Pediatrics, Division of Infectious Disease, Immunology & Allergy, University of Ottawa, Ottawa, ON, Canada

² Children's Hospital of Eastern Ontario, Ottawa, ON, Canada

³ Department of Radiology, University of Ottawa, Ottawa, ON, Canada

⁴ Ottawa Hospital Research Institute, Ottawa, ON, Canada

⁵ Department of Radiology, University of Manitoba, Winnipeg, MB, Canada

⁶ St. Boniface General Hospital, Winnipeg, MB, Canada

⁷ Département de radiologie, radio-oncologie et médecine nucléaire, Université de Montréal, Montréal, QC, Canada

⁸ Institut de Cardiologie de Montréal, Montréal, QC, Canada

⁹ Canadian Association of Radiologists, Ottawa, ON, Canada

¹⁰ Infectious Diseases and Immunity in Global Health Program at the Research Institute of the McGill University Health Centre, Montreal, QC, Canada

¹¹ Departments of Radiology and Epidemiology, University of Ottawa, Ottawa, ON, Canada

¹² Department of Medicine, University of Alberta, Edmonton, AB, Canada

¹³ Department of Medicine and Department of Biomedical and Molecular Sciences, Queen's University, Kingston, ON, Canada

¹⁴ Department of Radiology, Dalhousie University, Halifax, NS, Canada

¹⁵ Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada

Corresponding Author:

Adam Byrne, Department of Infectious Disease, Immunology & Allergy, Children's Hospital of Eastern Ontario, 401 Smyth Road, Ottawa, ON K1H 8L1, Canada.

Email: adbyrne@cheo.on.ca

urticaire, ou élevée, par exemple, une réaction anaphylactique. De nouvelles données probantes révèlent que les protocoles de prétraitement traditionnels, comme l'administration de diphenhydramine et de corticostéroïdes, ne sont pas efficaces et peuvent potentiellement causer des effets secondaires et autres préjudices. En outre, les données d'efficacité sur lesquelles cette pratique est basée sont faibles et obsolètes. Un groupe de travail composé de représentants de l'Association canadienne des radiologistes et de la Société canadienne d'allergie et d'immunologie clinique a été constitué dans le but d'informer les professionnels de la santé et les personnes établissant les politiques hospitalières au sujet des réactions d'hypersensibilité aux produits de contraste. Les objectifs du groupe de travail étaient de fournir une vue d'ensemble de l'épidémiologie, de la physiologie, des facteurs de risque et des types de réactions d'hypersensibilité; de synthétiser les données probantes concernant les stratégies de prétraitement qui réduisent le risque d'une réaction de rupture au minimum lié à l'utilisation de produits de contraste iodés et d'agents de contraste à base de gadolinium; d'examiner les tests d'allergie auxquels l'on a recours pour évaluer les patients ayant des antécédents de réaction d'hypersensibilité sévère; et de fournir une vue d'ensemble des lignes directrices existantes. Après avoir évalué les données probantes existantes, le groupe de travail a établi des recommandations basées sur un consensus, lesquelles se trouvent dans le présent guide pratique.

Keywords

allergy, hypersensitivity, iodinated contrast media, gadolinium-based contrast agents

Introduction

Contrast media are commonly administered pharmaceuticals and includes iodinated contrast media (ICM) and gadolinium-based contrast agents (GBCA).^{1,2} Although these pharmaceuticals have excellent safety profiles, a minority of the population may experience a hypersensitivity reaction (HR) following intravascular administration.^{3,4} HRs can be immediate or delayed, and range from mild, such as urticaria, to severe, including anaphylaxis.^{5,6} There is uncertainty regarding the safety of a repeat contrast media injection in patients with a history of HR, and the efficacy of premedication.⁷ Historically, the risk of a repeat HR in medical imaging departments was mitigated either by administering pretreatment protocols or by withholding contrast media altogether. For decades, pretreatment protocols that included diphenhydramine and corticosteroids were administered to patients; however, recent evidence is challenging the utility of this approach.⁸⁻¹⁰ Although withholding intravenous contrast media altogether ensures there will be no HR, withholding intravenous contrast can substantially limit the diagnostic performance of computed tomography (CT) and magnetic resonance imaging (MRI).

This practice guidance is a joint collaborative effort by representatives from the Canadian Association of Radiologists (CAR) and the Canadian Society of Allergy and Clinical Immunology (CSACI). The joint CAR/CSACI working group on HRs was assembled to inform the medical community and hospital policies about HRs to contrast media and is comprised of members with interest and expertise in contrast media safety and evidence synthesis. In this practice guidance, we review the epidemiology, physiology, risk factors, and types of HRs associated with contrast administration, as well as evidence regarding pretreatment strategies to minimize the risk of a breakthrough reaction for ICM and GBCAs. Investigations used to evaluate patients with a history of HRs are summarized, and an overview of existing guidelines is provided. Following an appraisal of the evidence, working

group members established clinical recommendations by consensus.

Physiology and Classification of Contrast Reactions

Adverse reactions to contrast media is an umbrella term that encompasses a wide variety of clinical presentations and mechanisms. Reactions to ICM do not occur secondary to iodine, but rather to the contrast molecule itself. As such, the term “*allergy to iodine*” in reference to contrast media HRs should be abandoned.^{11,12} Reactions to contrast media can be divided into 2 large categories—the common physiologic or chemotoxic reaction, and the less common HR. HRs to ICM and GBCA can be categorized as immediate or delayed. Although adverse reactions to ICM and GBCA are uncommon, mitigating these events is important as these agents are administered to tens of thousands of Canadians daily.

Physiologic or chemotoxic reactions are side effects to contrast media and represent the majority of adverse reactions.^{3,13} These reactions occur because of specific molecular attributes of the medium, and though almost always self-limiting, can rarely affect multiple organ systems, including cardiotoxicity, neurotoxicity, and nephrotoxicity.³ Common physiologic reactions include a vasovagal reaction, altered taste sensation, restlessness, headache, nausea, dizziness, and paraesthesia. At the injection site, patients may experience warmth, cold, or pain. Physiologic reactions are both concentration and dose-dependent.¹³

Acute or immediate HRs occur within 1 hour of exposure and typically include both IgE-mediated and non-IgE-mediated reactions.^{10,14} IgE-mediated reactions occur when an IgE antibody forms to the contrast media, which can also function as a hapten when bound to larger proteins, and rests on IgE-receptors present on the allergy effector cells of the immune system (ie, mast cells and basophils). Contrast media, acting as an allergen, binds to the IgE antibody, leading to the activation of mast cells and basophils, which then release a variety of mediators.¹⁵⁻¹⁷ These mediators cause symptoms that range

from mild urticaria to anaphylaxis, which is associated with hypotension, bronchospasm, and cardiovascular compromise.¹⁸ Classification of HRs as mild, moderate, and severe are provided by the American College of Radiology, and are provided in Appendix A. Non-IgE-mediated reactions are often referred to as non-IgE-mediated anaphylaxis,¹⁹ formerly known as “anaphylactoid” reactions; these occur when a substance causes non-IgE mediated mast cell or basophil activation. Clinically, the difference between these 2 mechanisms is negligible,²⁰⁻²² and the same management is required for both, usually including second generation antihistamines for mild reactions, and intramuscular epinephrine and cardiorespiratory support for more severe reactions.

Delayed HRs occur hours to days after exposure, making them more challenging to recognize and diagnose. Delayed HRs are usually mild, and typically manifest as isolated skin reactions; a maculopapular exanthem is the most common drug hypersensitivity reaction to ICM.²³⁻²⁷ However, there are rare reports of severe cutaneous reactions to ICM, such as acute generalized exanthematous pustulosis (AGEP),²⁸⁻³¹ drug reaction with eosinophilia and systemic symptoms (DRESS), and Stevens-Johns syndrome/Toxic Epidermal Necrolysis (SJS/TEN).³²⁻³⁴ These hypersensitivity reactions are T-cell mediated, as summarized in Sullivan et al.³⁵

Frequency of Contrast Reactions

Current estimates of acute adverse reactions to modern low osmolar contrast media (LOCM), including both physiologic and immediate HRs, range between 0.2% and 0.7%.^{3,36} Delayed HRs to LOCM occur less frequently than immediate HRs. An analysis of 11 712 796 LOCM administrations over a 3-year period resulted in 44 467 acute HR (0.38%) compared to 5725 delayed hypersensitivity reactions (0.05%).²⁵ Importantly, only 2409 (0.02%) immediate HRs were severe.²⁵

Reactions to GBAs range from 0.07% to 2.4% of administrations.³ The majority of adverse events are mild physiologic reactions, whereas HRs occur in less than 0.4% of contrast uses.³⁷⁻⁴¹ In one meta-analysis of 716 978 GBA administrations, HRs were observed in as few as 0.0009% of cases.⁴¹ Anaphylaxis to GBA is extremely rare; although previous ACR guidelines quoted a rate of 0.001% to 0.01%,⁴⁰ more recent studies suggest that anaphylaxis is far less common at 0.00003% to 0.004%.^{3,40-42} Delayed HRs are reported to occur in 0.05%,⁴³ with 99% of presentations involving urticaria or another skin reaction, and 46% of cases appearing on the day of administration.

Risk Factors

Multiple factors for increased risk of reactions to ICM and GBA have been reported. However, it should be noted that most patients with these risk factors will have no reaction after being administered ICM or GBA.³⁶ The most consistent risk factor that may predict a hypersensitivity reaction to

LOCM is a history of previous HR to iodinated contrast media.⁴⁴⁻⁴⁷ Other risk factors have been found, although there is inconsistency in reporting.³⁶ Additional risk factors include a history of atopy (asthma, previous drug reactions), female gender, concentration of the contrast, and injection rate of administration.^{36,44-46}

Risk factors for HRs to GBA are similar to ICM. Patients with a history of HRs to contrast media (including ICM) or asthma have a 1.5 to 3 times higher risk of reacting to a GBA.^{38,40,42,48,49} Patients with a prior HR to a GBA have a higher risk of recurrence with re-exposure, ranging between 21% and 60%.^{48,50,51} Some have reported higher rates of HRs in females compared to males, although males may have worse outcomes if they experience a severe reaction.^{38,42,49} One study from 1995 suggested that higher rates of injection may be linked to increased risk, but this has not been corroborated with newer research looking at modern agents.⁴⁸

Evidence Synthesis: ICM

From the 1950s to late 1990s, hyperosmolar ionic diatrizoic acid-based contrast (HOCM) was the main agent used for diagnostic imaging.⁵² HOCM was associated with a high adverse event rate of 5% to 15%.³ Consequently, prophylactic premedication protocols were devised to reduce the risk of an adverse reaction to HOCM. Greenberger et al developed a protocol of 3 doses of 50 mg oral prednisone every 6 hours, with a single intramuscular injection of diphenhydramine 50 mg.⁵³ In a cohort of 284 patients with a history of allergic reaction to HOCM, this prophylaxis was administered prior to 318 contrast procedures, leading to 24 breakthrough reactions. This protocol has formed the basis of department policies up to the present day, despite the study being limited by the lack of a control group and the use of HOCM. Lasser et al evaluated a 2-dose corticosteroid-only regimen in a multi-institutional randomized controlled trial of 6763 patients.⁵⁴ Although the authors found that the methylprednisolone preparation reduced the rate of all reactions ($P < .0001$), results from this study are not applicable to present-day practice because it evaluated HOCM. Moreover, the authors likely confounded physiologic reactions as HRs, and did not control for patients with a previous history of HR to HOCM in the randomization process.

With the arrival of non-ionic low-osmolar contrast media (LOCM), hypersensitivity rates dropped significantly. In a landmark national study from Japan, Katayama et al found adverse reaction rates of 12.66% and 3.13% for HOCM and LOCM, respectively, and that adverse reactions in the LOCM group were also less severe.⁵⁵ Importantly, some of the most common adverse drug reactions reported by Katayama et al are now recognized as physiologic reactions, such as flushing and nausea.⁵⁵

Although Greenberger and Patterson⁵⁶ and Lasser et al⁵⁷ re-tested their premedication protocols for LOCM, their results are difficult to interpret due to study design. In a non-randomized, non-controlled prospective study of 191 patients

and 200 contrast procedures, Greenberger et al premedicated patients with a history of adverse reaction to HOCM prior to receiving LOCM and found one breakthrough reaction. This result likely reflects the superior safety profile of LOCM as demonstrated by Katayama et al,⁵⁵ and not the efficacy of the premedication protocol. In a randomized controlled trial of 1155 patients, of whom only 107 had a history of HR, Lasser et al exposed patients to LOCM with or without premedication and demonstrated protection against mild reactions (0.2% with steroids compared to 1.9%, $P=.004$) but found no effect for more severe reactions.⁵⁷

Efficacy and Risks of ICM Premedication Protocols

Premedication with an antihistamine alone has been proven effective if the index reaction was mild.^{47,58,59} A review of 196 081 patients receiving contrast determined that premedication with antihistamines was associated with a decreased risk of a breakthrough reaction (OR, 0.53; 95% CI: 0.33, 0.86; $P=.01$), although the severity of initial HR is unavailable.⁴⁷ In a study of 850 patients with a previous HR to contrast, premedication was provided based on severity of reaction; there was no reported benefit in patients with a history of mild reactions being treated with antihistamines and corticosteroids as opposed to just antihistamines.⁵⁸ In another study of 1178 patients with history of mild HR to contrast, premedication with antihistamines decreased recurrence rates from 16.6% on reexposure to 10.7% (OR, 0.569; 95% CI: 0.443, 0.731; $P<.001$),⁵⁹ though a combination of antihistamine use with ICM agent switching was even more effective. Interestingly, the Mayo Clinic in Rochester Minnesota has abandoned the requirement for premedication in patients with a history of isolated urticaria based on a small study from their institution showing no benefit with antihistamines.^{60,61}

Appendix B provides information regarding the antihistamines currently available in Canada. The CSACI does not recommend first generation antihistamines, but rather second and third generation antihistamines are strongly preferred due to most having a faster speed of onset and significantly lower side effect profile. As of publication, the only intravenous antihistamine available in Canada is a first-generation antihistamine.

Recent studies have not shown strong evidence that premedication with corticosteroids prevents HRs to LOCM,^{58,60,62-64} especially for protection against breakthrough reactions.^{61,65-67} Mervak et al calculated that the number needed to treat to prevent one reaction of any severity in patients with a history of HR was 69 (95% CI: 39-304) and for severe reactions, 569 (95% CI: 389-1083).⁶⁵ After combining Mervak et al's⁶⁵ data with data from 2 other studies,^{68,69} Davenport and Cohan estimated the number needed to treat to prevent a single lethal reaction was 56 900 (95% CI: 38 900-108 300).⁶²

Premedication may also be associated with indirect costs and harms.⁶⁹ In a propensity matching study with a paired control group adjusted for known confounders, Davenport

et al showed that a premedicated cohort of inpatients had a longer median length of in-hospital stay (25 hours longer, $P<.001$) compared to the control group, and experienced longer delays before undergoing contrast-enhanced CT (25 hours longer, $P<.001$).⁶⁹ Using hypothetical analyses from their data and existing references, the authors projected that the use of oral 13-hour corticosteroid and diphenhydramine premedication would result in 551 hospital-acquired infections, 32 infection-related deaths, and significant added costs for each prevented death from an allergic-like reaction in patients with a prior allergic-like reaction to ICM.⁶⁹

This study highlights an important consideration that short-term (ie, less than 30 days) oral corticosteroids are known to carry some risk, including increased risk of fracture, sepsis and venous thromboembolism.⁷⁰ A multicentre study found that the relative risk of avascular necrosis after a short course of oral steroids in steroid-naïve patients was 1.60 (95% CI: 1.34-1.84).⁷¹ A short-term course of oral steroids for asthma management in some pediatric age groups was also associated with an increased risk of bone fracture (OR, 1.17; 95% CI: 1.04-1.33).⁷²

The time delay and costs associated with premedication may be reduced with an accelerated protocol. In 2017, Mervak et al performed a retrospective non-inferiority cohort study comparing an accelerated 5-hour IV corticosteroid protocol to the routine oral 13-hour regimen.⁷³ Two important conclusions were found: (1) the breakthrough reaction rate with 5-hour IV premedication (2.5%) was non-inferior to the traditional 13-hour oral regimen (2.1%); and (2) neither regimen prevented all moderate and severe breakthrough reactions. This study was the first since 1986⁷⁴ to re-evaluate the efficacy of urgent IV corticosteroid premedication, which was based on a series of 10 patients who received HOCM and different IV premedications.

Efficacy of ICM Agent Switching

To reduce the risk of a breakthrough reaction in patients with a history of HR to ICM, studies have evaluated the utility of administering a different ICM than the culprit agent. One study found breakthrough immediate reaction rates of 61/220 (27.7%) and 47/271 (17.3%) in patients without and with premedication, respectively.⁷⁵ By switching the LOCM, the breakthrough reaction rates were substantially reduced to 3/38 (7.9%) and 5/172 (2.9%) without and with premedication, respectively. Although these rates were not significantly different ($P=.15$), the sample sizes were low.⁷⁵ In a cohort of 1973 high-risk adult and pediatric patients that underwent 4360 contrast-enhanced CTs, McDonald et al found that premedication with steroids was ineffective in preventing breakthrough reactions. After adjusting for potential confounders such as age, reaction severity, and sex, they found reactions rates as follows: same ICM with premedication, 80/423 (19%); same ICM without premedication, 111/745 (15%, $P=.12$); different ICM with steroid premedication, 5/155 (3%, $P<.001$); and different ICM without premedication,

Table 1. Types of Iodinated Contrast Media and Common Side Chain Structures.

		N-(2,3-dihydroxypropyl) carbamoyl side chain	
		Present	Absent
N-(2,3-dihydroxypropyl)-N-methyl-carbamoyl side chain	Present	Iopromide (Ultravist)	Iobitridol (Xenetix)
	Absent	Iohexol (Omnipaque)	Iopamidol (Isovue)
		Iomeprol (Iomeron)	
		Ioversol (Optiray)	
		Iodixanol (Visipaque)	

10/322 (3%, $P < .001$).⁶¹ This study was later included in a systematic review and meta-analysis by Umakoshi et al examining breakthrough reactions to ICM in 7155 adult patients.⁷⁶ They found that switching the ICM reduced the risk of breakthrough reactions by 61% (risk ratio=0.39, 95% credible interval: 0.24, 0.58). Additionally, they also noted that premedication did not impact the risk of a repeat reaction, although most patients who were premedicated received only antihistamines alone or shortened corticosteroid protocols.⁷

A few studies have evaluated baseline reaction rates of ICM agents, and the optimal contrast-switching strategy based on breakthrough reaction rates for different agents. A large study from the Mayo clinic found that patients who received iohexol had a lower rate of acute HR (1047/344 979, 0.30%) compared to patients who received iopromide (81/9687, 0.84%, $P < .001$), but not compared to patients who received iodixanol (22/5311, 0.41%, $P = .61$).³⁶ Another large study from Korea found lower adverse reaction rates with iohexol (9041/3 816 072, 0.24%), ioversol (3725/1 592 523, 0.23%), and iopamidol (8853/2 333 794, 0.38%); higher rates were found with iopromide (7734/1 310 393, 0.59%) and iomeprol (0.70%).²⁵

In a recent multicenter retrospective study, Kim et al evaluated the optimal ICM switching strategy in 1066 patients with a history of HR.⁷⁷ After adjusting for age, sex, prior HR severity, and use of premedication, they found that ICM switching with an agent with a chemical structure similar to the culprit agent did not reduce the risk of a repeat HR (OR, 0.98; 95% CI: 0.64–1.50). ICM substitution with an agent with a different chemical structure reduced the risk (OR, 0.51; 95% CI: 0.37–0.69). The findings from this study are congruent with a skin test study which found that, in patients with history of severe HR, the skin-test cross-reactivity rate between ICM agents was associated with sharing of a common side chain, and recurrence rates were significantly reduced by avoiding an agent with a common side chain.⁷⁸ Table 1 shows the ICM available in Canada according to the sidechain structure.

Evidence Synthesis: Gadolinium-Based Contrast Agents

Shown in Table 2 are the GBCAs available in Canada according to their molecular structure. The type of GBCA has been associated with the risk of having an adverse reaction. Macrocyclic and linear ionic agents have an increased rate of HRs compared to linear nonionic agents, although

the occurrence rate of HRs to all GBCAs is very low.^{38,41,42,79} A meta-analysis from 2017 found the following reaction risk per 10 000 injections: macrocyclic agents, 14 (95% CI: 12–16); linear ionic agents, 8.3 (95% CI: 7.5–9.2); and linear nonionic agents, 1.5 (95% CI: 0.74, 2.4).⁴¹ The same study found that GBCAs with protein-binding of chelates (see Table 2) were also independently associated with an increased risk of adverse reactions.⁴¹ Unfortunately, many of the agents with higher kinetic stability, considered less likely to cause nephrogenic systemic fibrosis and gadolinium deposition (ie, macrocyclic agents, gadoxetate disodium) fall into these higher risk categories for HRs.^{2,80}

Few studies have evaluated the risk of breakthrough reaction with premedication protocols or contrast switching for GBCAs, and historically practice has generally followed that for ICM. In a 2020 systematic review and meta-analysis, Walker et al included 23 studies dating back to 1990, but the study included only 120 patients and 130 GBCA administrations.⁸¹ Using meta-regression, the authors found high estimates of breakthrough reaction rates, as follows: overall, 37/103 (39%; 95% CI: 30%–49%); and after contrast switching, 4/9 (40%; 95% CI: 15%–72%) with and 4/5 (71%; 95% CI: 25%–75%) without corticosteroid premedication.

Subsequent studies have found much lower breakthrough reaction rates and a benefit to GBCA switching. Ryoo et al evaluated 185 patients with a history of mild acute HR who were re-exposed to 397 GBCA administrations, some of whom received intravenous chlorpheniramine (a first-generation antihistamine) 30 minutes prior to the exam or a combination of intravenous chlorpheniramine and methylprednisolone.⁵¹ They found no difference in the breakthrough reaction rate between the premedicated (61/299, 20.4%) and non-premedicated groups (17/98, 17.3%; $P = .51$). However, breakthrough reaction rates were reduced from 69/267 (25.8%) in patients re-exposed to the same GBCA to 9/130 (6.9%, $P < .001$) in patients who received a different GBCA. In a prospective efficacy trial, Walker et al evaluated 26 patients with history of mild ($n = 24$) or moderate ($n = 2$) HR to GBCA.⁸² Contrast switching resulted in a single mild breakthrough reaction, corresponding to a rate of 1/27 (3.7%; 95% CI: 0.09%–18.9%). There was no difference between patients with (1/16, 6.3%; 95% CI: 0.15%–28.7%) or without (0/11, 0%; upper bound 95% CI: 25.0%) corticosteroid premedication.

Recently, Ahn et al found a HR rate of 1304/331 070 (0.4%) GBCA administrations in 154 539 patients, of which 1178

Table 2. Categories of Gadolinium-Based Contrast Agents.

	Linear	Macrocylic
Nonionic	None	Gadobutrol (Gadovist) Gadoteridol (ProHance)
Ionic	Gadopentetate dimeglumine (Magnevist) Gadoxetate disodium (Primovist)* Gadobenate dimeglumine (MultiHance)*	Gadoterate meglumine (Doteram)

Note. Linear: Uses a linear ligand which does not completely surround the gadolinium ion. Macrocylic: A cage-like ligand which completely surrounds the gadolinium ion with nitrogen. Nonionic: Neutral charge. Ionic: Electrically charged.

*Transiently bind plasma proteins.

HRs were acute.⁴⁰ Of these, there were 1445 repeat exposures of GBCA in 487 patients with a history of acute or delayed HR to GBCA. Including both acute and delayed HRs, the following breakthrough reaction rates were found: same GBCA with no premedication, 37/118 (31.4%); same GBCA with premedication, 149/786 (19.0%); different GBCA with no premedication, 6/100 (6.0%); and different GBCA with premedication, 21/441 (4.8%). An analysis that adjusted for age and sex derived odds ratios for a repeat reaction of 0.6 (95% CI: 0.4–0.9; $P < .023$) with two-dose premedication only, 0.3 (95% CI: 0.2–0.5; $P < .001$) with changing the contrast agent, and 0.1 (95% CI: 0.06–0.2; $P < .001$) with both interventions.

Overview of Existing Guidelines

A summary of guidelines from other societies specific to iodinated contrast is provided in Table 3. There is a lack of consensus in the medical imaging and allergy communities regarding the optimal method to minimize the risk of HRs.

Several societies do not recommend the use of steroids. The 2020 Joint Task Force on Practice Parameters for Allergy and Immunology state: “We suggest against routinely administering glucocorticoids and/or antihistamines to prevent anaphylaxis in patients with prior radiocontrast HRs (conditional recommendation, certainty rating of evidence: very low),” and “Higher certainty evidence is needed to better inform practice.”⁶⁴ The current European Society of Urogenital Radiology (ESUR) guidelines state: “Premedication is not recommended because there is not good evidence of its effectiveness.”⁹ Given the paucity of high-quality evidence, the ESUR and the European Academy of Allergy and Clinical Immunology (EAACI) no longer recommend premedication for acute HRs to LOCM.^{9,10} These societies recommend switching contrast agents instead of premedication alone due to the growing evidence supporting this practice.^{67,76}

The Royal College of Radiologists (RCR—UK) and the Royal Australian and New Zealand College of Radiologists (RANZCR) also suggest contrast switching, but still recommend premedication.⁸³ There is no consensus whether contrast switching should include premedication⁷⁶; some authors recommend both strategies.⁸⁵ The ACR 2023 Contrast Media Manual recommends premedication with steroids and antihistamines, but also suggests that contrast switching may be

more effective at preventing adverse reactions than premedication alone. Some experts believe the ACR guideline should be updated based on newer evidence.⁷

Special Considerations of Hypersensitivity Reactions to Contrast Media (GBCA and ICM)

Premedication for Delayed and Severe Reactions

Based on the limited available data, though some authors have reported its effectiveness,⁸⁶ premedication for delayed HRs is not recommended.^{3,9,10,87} It is therefore essential to document the onset of a patient’s index reaction to avoid unnecessary premedication and better understand the type of reaction presented by the patient.

There is no high-quality evidence supporting premedication to prevent an anaphylactic reaction. The 2020 Joint Task Force on Practice Parameters “suggest against routinely administering glucocorticoids and/or antihistamines to prevent anaphylaxis in patients with prior radiocontrast [hypersensitivity reactions] when readministration of a low- or iso-osmolar, non-ionic [radiocontrast media] agent is required.”⁶⁴ For anaphylactic reactions, an allergy consultation should be considered before re-exposure to contrast media, depending on access to an allergist and urgency of medical imaging.

Non-Vascular Contrast Media

Although LOCM has completely replaced HOCM for intravascular use, HOCM is still used alongside LOCM formulations for enteric examinations. Adverse reactions secondary to non-vascular ICM (LOCM and HOCM) are quite rare and reported primarily in case reports.^{3,88} Premedication for non-vascular ICM use in previous intravascular reactors is not specifically addressed in the ACR Contrast Media Manual 2023.³ ESUR 10.0 states that “[w]hen absorption or leakage into the circulation is possible, take the same precautions as for intravascular administration.”⁹ In his review, Davis reported a variety of severe, yet quite rare, adverse reactions to non-vascular contrast. Rectal contrast appears to be unique in that no severe reactions were reported with the use of contrast enemas.

Table 3. A Summary of Guidelines From Other Societies Specific to Iodinated Contrast Media.

Society guideline	Acute hypersensitivity reactions		Delayed hypersensitivity reactions	
	Prevention	Investigations	Prevention	Investigations
European Society of Urogenital Radiology (2019) ⁹	Use a different contrast agent. Prophylaxis not recommended.	Consider serum histamine and tryptase collection during and after the reaction. SPT/ID testing 1-6 mo after the event.	Use an alternate contrast agent; base this choice on investigations. Prophylaxis is not recommended.	Consider patch testing. Consider ID testing with delayed interpretation.
European Academy of Allergy and Clinical Immunology (2020) ¹⁰	Use an alternate contrast agent, as guided by investigations. Prophylaxis is not recommended (can be considered if previous contrast trigger not identified, or if testing not complete in an emergency).	Consider serum tryptase during and after the reaction. SPT/ID testing 2-6 mo after the event. Consider use of BAT. Consider drug provocation if favourable risk/benefit ratio.	Use an alternate contrast agent, as guided by investigations. Prophylaxis is not recommended.	Any patient with a maculopapular exanthem should be investigated. Tests to consider include patch testing, ID testing, or LTT.
American Academy of Asthma, Allergy, and Immunology: Anaphylaxis practice parameter update (2020) ⁶⁴	Prophylaxis is generally not recommended (for LOCM contrast), though there may be conditional exceptions, including high level of perceived risk of anaphylaxis fatality, though evidence is lacking to support this approach.	No recommendations made	Prophylaxis may be of some benefit in patients with severe reactions.	Delayed ID may be considered, though preference would be to simply avoid prior triggering media.
American College of Radiology (2023) ³	Prophylaxis (steroids, antihistamines) is recommended combined with changing the class of agent.	No investigations are recommended.	Prophylaxis may be of some benefit, though there is no specific recommendation. Consider alternate contrast agent.	No investigations are recommended.
Royal Australian and New Zealand College of Radiologists (2018) ⁸³ Endorsed by the Royal College of Radiologists (UK) ⁸⁴	Premedication with corticosteroids, with or without antihistamines has been shown to reduce the likelihood and severity of anaphylactic reactions but there is no evidence that it reduces the likelihood of death resulting from a breakthrough anaphylactic reaction.	No investigations are recommended.	The effectiveness of premedication with corticosteroids in reducing the incidence of recurrent delayed contrast media reaction is unknown.	No investigations are recommended.
Korean Academy of Asthma, Allergy and Clinical Immunology (2022) ⁸⁵	Avoid use of contrast if possible. If contrast to be used, use alternate agent with prophylaxis, if testing previously unavailable. If previously investigated, use alternate contrast choice. Prophylaxis, in general, is not recommended.	SP/ID testing with trigger ICM and alternates. Consider IV DPT challenge to alternate media if needed.	If severe, avoid contrast if possible. If impossible, base alternate choice on allergy testing if favourable risk-benefit ratio. All patients with non-severe reactions should use alternate ICM if urgent, or complete testing if time allows. Prophylaxis, in general, not recommended, but may be considered if high risk individuals with severe HR's.	Consider intradermal or patch testing. May also consider DPT with test-negative alternates.

Given the rarity of HRs despite the widespread use of enteric contrast, and lack of evidence to support premedication, the working group does not endorse premedication for non-vascular contrast media administration. Contrast switching should be considered in the rare event of a patient with history of HR to non-vascular contrast.

Pediatric Population

Compared to adult patients, pediatric patients have lower rates of hypersensitivity reactions to LOCM and GBCA. A study in 2022 comparing HR rates to iopromide found a reaction rate of 0.47% for children compared to the adult rate of reaction of 0.74%.⁸⁹ The adjusted odds ratio for HR to contrast for children compared to adults in this study was 0.58 (95% CI: 0.34-0.98, $P < .043$).

A review of pediatric HRs to contrast media by Dillman et al demonstrated that the rate of HRs to GBCA in children is also very low.³⁷ In this study, GBCA HRs occurred in only 6/13 344 (0.04%) children and 48/65 009 (0.07%) adults. The relative risk of reaction in adults was 1.53 (95% CI: 0.66-3.56) compared to children, and was not significant.

Premedication considerations for children are similar to adults, with doses adjusted for weight. Findings from a survey of the Society of Chairs of Radiology in Children's Hospitals (2011) found that most pediatric centres currently follow premedication guidelines, with 93% of those protocols using steroids as preventative treatment, and 80% using first generation antihistamines.⁹⁰ However, exact dosing regimens and timing of administration were quite variable. A systematic review by Aljebab et al concluded that the effects of short-course corticosteroid premedication (<14 days) for children for any cause, not

just ICM pre-treatment, is not without potential side effects and harms, including vomiting, behavioural changes and mood swings, sleep disturbance and most important, infections secondary to immunosuppression.⁹¹

Importance of Documentation

To implement contrast switching, the culprit agent must be known. Unfortunately, practice patterns for documenting HRs vary and many centres lack proper documentation. In their review, Deng et al could not determine the culprit agent in 35 992/40 669 (88.5%) of contrast reactions.⁹² Likewise, McDonald et al could not retrospectively identify the culprit agent in 1348/1973 (68%) of patients.⁶¹ Simply documenting an allergy/reaction to “iodine” or “gadolinium” is insufficient.

It is paramount to document the precise name of a specific contrast media agent that causes a HR. The symptoms, severity (mild, moderate, severe), acuity (acute vs delayed), treatment, and outcome of the reaction should all be documented in the patient’s electronic health record. For ease of reference and to assist radiologists when protocolling future imaging requisitions, the nature of the HR and specific contrast agent should also be included the patient’s imaging examination report, which is sent to the referring healthcare provider and stored on the electronic medical record and Picture Archive and Communication System (PACS).

Fasting Prior to Intravascular Contrast Media

Some institutions instruct patients to fast prior to receiving intravascular contrast media in order to reduce the likelihood of vomiting and aspiration.³ However, the risk of vomiting with modern contrast agents is very low, and fasting has not been shown to improve patient safety.⁹³⁻⁹⁶ In addition, fasting is an inconvenience with potential risks, such as missed medications and hypoglycemia in patients with diabetes. As such, the working group recommends that patients not be instructed to fast prior to receiving intravascular contrast, unless required for the procedure (eg, CT or MR enterography).

Investigations for Hypersensitivity Reactions

Anaphylaxis is a clinical diagnosis based on symptom presentation and the timing of the reaction in relation to the triggering exposure. Several biomarkers for anaphylaxis can be measured, as referenced in Appendix C. During an immediate HR, the measurement of serum tryptase is the easiest and most practical biomarker to collect in Canada, as other options are rarely available. Serum tryptase will increase 30 minutes after an immediate HR and remain elevated for several hours before returning to baseline. These results can take time to return and must be compared to baseline tryptase concentrations to determine if activation of mast cells occurred, and therefore, are not helpful during the HR, but can be helpful when later assessed by an allergist.

A summary of investigations for evaluation of contrast media hypersensitivity is provided in Appendix D. Allergists often use

skin prick testing and intradermal testing to investigate possible immediate HRs. As many HRs do not involve IgE-mediated mechanisms, skin prick testing has poor sensitivity. Over 90% of patients who have had an immediate HR will test negative on skin prick testing, and approximately 50% to 90% will be negative on intradermal testing, depending on the severity of the reaction.^{15,97} Despite this, many guidelines still recommend skin prick testing and intradermal testing to investigate HRs. For example, the EAACI position paper published in 2020 suggests a broad panel of ICM for testing to identify potential triggers. To support this approach, Bansie et al reviewed 19 studies that examined patients with a history of immediate HRs to ICM.⁹⁸ If a patient tested positive for an offending agent on skin prick testing, an alternate agent that had tested negative was used without reaction in 94% of cases. This paper does note that it was rare for patients who tested positive for an ICM to be summarily challenged to the same ICM; out of 7 patients who were re-exposed to a ICM after testing positive on investigations, 6 had a second HR. Similar results were reported with GBCAs, with provocation challenges to alternate GBCA after testing positive to one agent resulted in no adverse events.

As a counterpoint, Lee et al investigated the use of intradermal testing for ICM reagents prior to contrast exposure.⁹⁹ 2918 patients were pre-tested, with 15 patients having a positive test. All 15 of these patients were challenged with the agent that had resulted in a positive test, and all 15 patients had no reaction. That said, 19 patients in this cohort did have a hypersensitivity reaction but had tested negative prior to the reagent being administered. The authors concluded that routine intradermal testing before the administration of a contrast agent resulted in a sensitivity and positive predictive value of 0%.

Delayed hypersensitivity reactions have been investigated with delayed intradermal testing and patch testing. The specificity of delayed intradermal testing has been calculated at 100%^{15,97,100} and the negative predictive value of a negative skin test and challenge has been calculated at 90% to 96% in some clinical studies.^{98,101-103} However, the sensitivity and test accuracy are unknown at this time.⁹⁷ A meta-analysis demonstrated that allergy investigations were positive in 16.9% to 53.5% of cases with positive provocation following skin testing in 0% to 34.6% of the cases.^{98,99}

Drug provocation testing, through IV challenge, is the most accurate of investigations, though this carries a risk of provoking a repeat reaction and is logistically difficult for most allergy clinics to organize, especially outside of a hospital setting.¹⁰⁴ The use of drug provocation tests is recommended in limited and controlled circumstances following a patient risk-benefit discussion.

Basophil activation testing results in higher specificity and sensitivity for the investigation of immediate hypersensitivity reactions; however, this test has limited availability and is used more often in research than in clinical laboratories.

Access to Allergists in Canada

The CSACI estimates that there are approximately 350 allergists actively practicing in Canada as of 2024 (personal

communication). Most of these allergists are in community practices without access to hospitals and associated resources, including availability of contrast media. The wait times for allergists vary significantly across the country and consults for new assessments of a contrast hypersensitivity may take as long as 6 to 12 months for a complete assessment. As most HRs (mild, moderate) can be managed without the need for allergy consultation or investigations, only patients with history of severe HR, including serious delayed reactions such as SJS/TEN or DRESS, should be considered for allergy referrals.

Should Allergists Routinely Investigate Hypersensitivity Reactions?

For patients with a history of HR to contrast media, the EAACI guidelines¹⁰ recommend skin prick and intradermal testing for both the suspected and alternative contrast agents, ideally 2 to 6 months post-reaction. Negative results should be followed by a direct provocation challenge. Skin prick testing uses undiluted contrast (300-320 mg/mL), while intradermal testing uses a 1:10 dilution. Various challenge protocols exist in the literature; a recent paper indicated a two-step challenge with 5 and 30 mL dose separated by 15 minutes can successfully identify patients potentially having an IgE-mediated reaction to contrast media.¹⁰⁵ As outlined above, the evidence supporting various testing protocols are weak and unclear. Accurate positive predictive value assessments are difficult due to the rarity of severe reactions and limited patient reexposure data in patients with positive testing. While useful in rare cases (eg, severe reaction to unknown LOCM, or multiple contrast reactions), we do not recommend routine skin or intradermal testing over contrast switching due to weak supporting evidence and limited resources, though allergists with established protocols may still choose to use them.

Conclusions

Contrast media agents have excellent safety profiles, and HRs are uncommon. In this guidance, the joint CAR-CSACI working group has reviewed the evidence and developed recommendations in consensus to assist health-care providers with updating departmental policies and protocols. Flowcharts for minimizing the risk of a breakthrough reaction in patients with a history of HR to known ICM or GBCA, and unknown ICM are provided in Figures 1 and 2, respectively. For patients with a history of HR to a specific contrast media agent, contrast switching is the single most effective measure to avoid a breakthrough reaction for both LOCM and GBCAs. There is some evidence supporting the use of antihistamines to prevent a mild reaction. However, evidence supporting the use of steroids to prevent a breakthrough reaction to LOCM is weak, and to prevent a breakthrough reaction to GBCAs is mixed. The use of steroids is also associated with risks. There is overall heterogeneity and a general lack of strong evidence supporting

premedication protocols, and further research including systematic reviews are required.

Recommendations

1. The dose and precise name of any contrast media must be documented in the patient's electronic health record, such that it can be easily retrieved in the event of an acute or delayed hypersensitivity reaction. If a patient experiences an acute contrast agent hypersensitivity reaction, the precise name of the offending contrast should also be documented in the patient's radiology report, which is sent to the referring provider and stored on PACS. The onset and nature of the reaction as well as treatment should also be documented. Ideally, a reporting mechanism should also be in place for delayed hypersensitivity reactions.
2. Patients (adults and pediatric populations) should only be considered at risk for a hypersensitivity reaction if they had a previous hypersensitivity reaction to the same type of contrast agent. That is, HR to LOCM ICM is a risk factor for future HR to LOCM ICM, and HR to GBCA is a risk factor for future HR to GBCA. There is insufficient evidence to support routine screening of other risk factors. It is important to distinguish between a true hypersensitivity reaction and a physiological reaction.
3. For patients with a history of a mild, moderate, or severe hypersensitivity reaction to ICM or GBCA, switching to a chemically different contrast agent is the single best protective measure to avoid a breakthrough reaction (Figure 1). For patients with a history of mild or moderate breakthrough reaction after contrast switching, a third agent should be administered. Contrast switching requires institutions and health authorities to have at least 2 different contrast agents. Single vendor contracts should allow for purchasing a second agent for this purpose.
4. For patients with a history of HR to ICM but the offending agent is not known, management is based on the date of the reaction (Figure 2):
 - If the reaction occurred before the year 2000, it can be reasonably assumed that the offending agent was not a low-osmolality contrast media (LOCM) agent, and the patient is then cleared to be administered LOCM administered without premedication.
 - If the reaction occurred on or after the year 2000, and the reaction was severe (acute or delayed), consider another imaging modality to answer the clinical question. Consider referral to an allergist if access and urgency of imaging allows. Premedication is not recommended.
 - If the reaction occurred on or after the year 2000, and the reaction was mild or moderate, consider premedicating with second generation antihis-

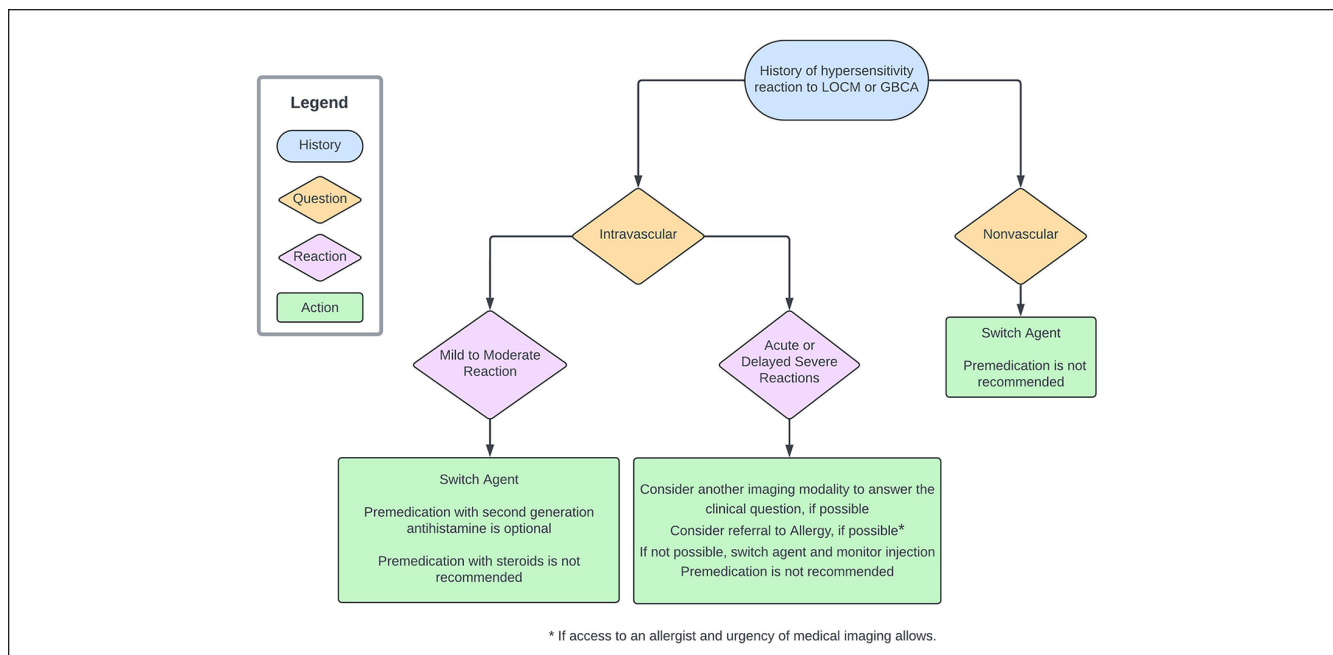


Figure 1. Hypersensitivity reaction to LOCM or GBCA.

Note. LOCM=low-osmolality contrast media; GBCA=gadolinium-based contrast agents.

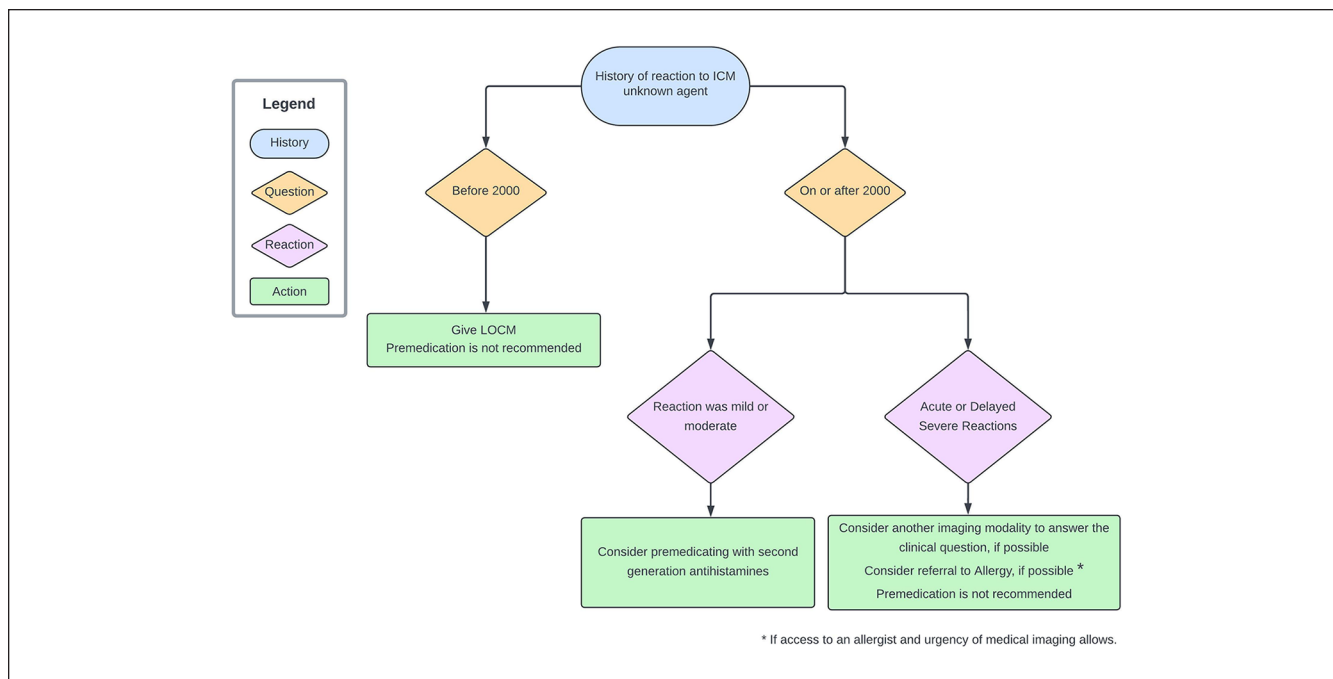


Figure 2. Hypersensitivity reaction to ICM unknown agent.

Note. ICM=iodinated contrast media.

- amines and monitoring the patient during and immediately after contrast media injection for any hypersensitivity reaction.
5. In patients with a history of hypersensitivity reaction to **LOCM iodinated contrast media**, premedication with steroids is not supported by high quality

research. What evidence exists is methodologically flawed and pertains to HOCM. Due to lack of efficacy and likely harms associated with steroid pre-treatment prophylaxis, the working group recommends against routine use of steroids in high-risk patients. This practice should be discontinued.

6. In patients with a history of hypersensitivity reaction to **gadolinium-based contrast agents**, premedication with steroids is not recommended. The evidence supporting steroid premedication to prevent a breakthrough reaction is mixed, but overall shows little benefit, with risk of potential harm.
7. Second-generation antihistamines can protect patients with history of mild hypersensitivity reaction from a breakthrough reaction. The added benefit of antihistamine after contrast switching is less clear and can be considered optional. Ideally, oral second-generation antihistamines should be given at least 1 hour prior to initiation of contrast.
8. At present, there is insufficient evidence to recommend one low-osmolality contrast media (LOCM) product over another to reduce hypersensitivity reactions. There is emerging evidence that contrast switching may be guided by the molecular structure of an agent, however, the working group considered this insufficient to make specific recommendations at this time.
9. Although there is some evidence regarding differences in hypersensitivity reactions for different gadolinium-based contrast agents, these differences are small and the overall risk of HR to GBCA is very low. The optimal choice of GBCA is based on additional factors, including cost, clinical indication, and T1 relaxivity.
10. For patients with a history of anaphylaxis to contrast media, the risk of a breakthrough reaction can be limited by switching to a different imaging modality, if diagnostically acceptable. If not, switching to a different contrast agent is recommended. The patient should be monitored during and after the contrast media injection. Premedication is not recommended.
11. For patients who experience an anaphylaxis reaction, once the patient has stabilized, collection of serum tryptase may help to determine if the reaction was an immediate hypersensitivity reaction. Serum tryptase should be collected 30 to 120 minutes after the onset of symptoms. Consider referring to allergy, when possible.
12. For patients with a history of hypersensitivity reaction to nonvascular contrast, contrast switching without premedication is recommended for future administrations of non-vascular or vascular contrast. Adverse reactions to non-vascular contrast media are limited to case reports and small series. Based on a lack of evidence and overall rarity of these events, the expert consensus recommends against a pre-medication protocol.
13. It is recommended that patients not be instructed to fast prior to receiving intravascular contrast media, unless required for the specific imaging examination (eg, CT or MR enterography).

Appendix A. American College of Radiology Categories of Acute Reactions.

Severity	Allergic-like (hypersensitivity)	Physiologic
MILD <i>Signs and symptoms are self-limited without evidence of progression.</i>	- Limited urticaria/pruritis - Cutaneous oedema - Limited "itchy"/"scratchy" throat - Nasal congestion - Sneezing/conjunctivitis/rhinorrhoea	- Limited nausea/vomiting limited - Transient flushing/warmth/chills - Headache/dizziness/anxiety/altered taste - Mild hypertension - Vasovagal reaction that resolves spontaneously
MODERATE <i>Signs and symptoms are more pronounced and commonly require medical management. Some of these reactions have the potential become severe if not treated.</i>	- Diffuse urticaria/pruritis - Diffuse erythema, stable vital signs - Facial oedema without dyspnoea - Throat tightness or hoarseness without dyspnoea - Wheezing/bronchospasm, mild or no hypoxia - Diffuse oedema, or facial oedema with dyspnoea - Diffuse erythema with hypotension - Laryngeal oedema with stridor and/or hypoxia - Wheezing/bronchospasm, significant hypoxia - Anaphylactic shock (hypotension + tachycardia)	- Protracted nausea/vomiting - Hypertensive urgency - Isolated chest pain - Vasovagal reaction that requires and is responsive to treatment - Vasovagal reaction resistant to treatment - Arrhythmia - Convulsions, seizures - Hypertensive emergency
SEVERE <i>Signs and symptoms are often life-threatening and can result in permanent morbidity or death if not managed appropriately. Cardiopulmonary arrest is a nonspecific end-stage result that can be caused by a variety of the following severe reactions, both allergic-like and physiologic. If it is unclear what etiology caused the cardiopulmonary arrest, it may be judicious to assume that the reaction is/was an allergic-like one.</i> <i>Pulmonary oedema is a rare severe reaction that can occur in patients with tenuous cardiac reserve (cardiogenic pulmonary oedema) or in patients with normal cardiac function (noncardiogenic pulmonary oedema). Noncardiogenic pulmonary oedema can be allergic-like or physiologic; if the etiology is unclear, it may be judicious to assume that the reaction is/was an allergic-like one.</i>		

Note. ACR Manual on Contrast Media. American College of Radiology; 2023. Accessed March 29, 2023. https://www.acr.org/-/media/acr/files/clinical-resources/contrast_media.pdf. Permission to reproduce granted by the American College of Radiology.

Appendix B

Antihistamines Currently Available in Canada

Antihistamines are divided into first, second, and third generation antihistamines largely based on their creation and side effect profile. Diphenhydramine is the first-generation antihistamine that is most widely known and has been available since 1946, which predates current safety and efficacy standards. Due to the higher risk of side effects with first generation antihistamines, including sedation, poor sleep quality, cardiac toxicity, respiratory

depression, coma, and death, second generation antihistamines were created that minimally cross the blood-brain barrier, have no anticholinergic effects, and significantly improved cardiac side effects. Third generation antihistamines are metabolites or enantiomers of other antihistamines, improving the safety and efficacy profile of these medications, which include fexofenadine and desloratidine. As per the CSACI, due to the suboptimal safety and efficacy profile, first generation antihistamines are no longer recommended for use, with later generation antihistamines being the strongly preferred choice.

Adapted from Fein et al.¹⁰⁶

Oral antihistamines	Time (h) to maximum plasma concentration after a single dose	Terminal elimination half-life (h)	Clinically relevant drug-drug interactions	Onset of action (h)	Duration of action (h)
First (old) generation antihistamines					
Chlorpheniramine	2.8 ± 0.8	27.9 ± 8.7	Possible	3	24
Diphenhydramine	1.7 ± 1.0	9.2 ± 2.5	Possible	2	12
Doxepin	2	13	Possible	NA	NA
Hydroxyzine	2.1 ± 0.4	20 ± 4.0	Possible	2	24
Second/third (newer) generation antihistamines					
Bilastine	1.2	14.5	Unlikely	2	24
Cetirizine	1.0 ± 0.5	6.5-10	Unlikely	0.7	≥24
Desloratidine	1.0-3.0	27	Unlikely	2-2.6	≥24
Fexofenadine	1.0-3.0	11.0-15.0	Unlikely	1.0-3.0	24
Levocetirizine	0.8 ± 0.5	7 ± 1.5	Unlikely	0.7	>24
Loratidine	1.2 ± 0.3	7.8 ± 4.2	Unlikely	2	24
Rupatadine	0.75-1.0	6 (4.3-14.3)	Unlikely	2	24

Appendix C. Commercially Available Biomarkers of Anaphylaxis.

Biomarker	Normal values	Test protocol	Pro	Cons	Citation
Serum tryptase	≤ 11.4 ng/mL	Draw 1-6 h after exposure to allergen, best 1-2 h after symptom onset.	High specificity No sample storage requirements	Negative in up to 40% of cases of anaphylaxis	Schwartz et al ¹⁰⁷ Sala-Cunill et al ¹⁰⁸
Serum Histamine	< 10 nmol/L	Levels peak 5-15 min after allergen exposure, returns to normal 10-30 min later.	High specificity	Sample requires freezing. Falsely elevated in histamine rich foods Short half-life 2 min	Oosting et al ¹⁰⁹ Hogan and Schwartz ¹¹⁰ van Doormaal et al ¹¹¹ Tomasiak-Łozowska et al ¹¹²
Urine N-methylhistamine	176 µmol/mol cr	Detectable within 30-60 min of anaphylaxis. Requires 24 h urine collection.	High specificity Sensitivity 0.81, specificity 0.93.	Falsely elevated in histamine rich foods. Normal values extrapolated from systemic mastocytosis patients.	Lin et al ¹¹³

Appendix D. Diagnostic Tests in Contrast Media Hypersensitivity.

Test	Test outcomes	Test protocol	Citation
Skin Prick Test—Immediate HR	3% positive	Read at 20 min Undiluted contrast media	Yoon et al ⁹⁷ Brockow et al ¹⁵
Skin Prick Test Non-immediate HR	7% positive	Read at day 2-3 Undiluted contrast media	Yoon et al ⁹⁷ Brockow et al ¹⁵
Intradermal Test— immediate HR	Positive rate higher when performed 1-6 mo following reaction. Mild reactions—12% positive Moderate reactions—16% positive Severe reactions—52% positive	Read at 20 min 1:10 dilution contrast media	Yoon et al ⁹⁷ Brockow et al ¹⁵
Intradermal Test—non immediate HR	22% positive	Read at days 1, 2, 3 1:10 dilution contrast media	Yoon et al ⁹⁷ Brockow et al ¹⁵
Patch test—Non immediate HR	16% positive	Read at 48 and 72 h Undiluted, soaked in filter paper	Yoon et al ⁹⁷ Brockow et al ¹⁵
Basophil Activation Test- Immediate HR	1:10 dilution has 61.5% sensitivity, 76.7% specificity 1:100 dilution has 50% sensitivity, 90.7% specificity	1:10 or 1:100 dilution contrast media	Pinnobphun et al ¹¹⁴
Drug Challenge—Immediate and non-immediate HR	93.1% of patients tolerate challenge to skin test negative contrast media		Schrijvers et al ¹⁰¹

Note. HR = hypersensitivity reaction.

Acknowledgments

The authors would like to thank the members of the Canadian Association of Radiologists and the Canadian Society of Allergy and Clinical Immunology who took the time to provide their feedback and peer review during the drafting of these guidelines.

Abbreviations

CT	computed tomography
HOCM	high-osmolality contrast media
HR	hypersensitivity reaction
ICM	iodinated contrast media
LOCM	low-osmolality contrast media
GBCA	gadolinium-based contrast agent
PACS	Picture Archive and Communication System

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Byrne has participated in advisory boards for ALK Abello, Miravo, Medexus, Bausch Health, and Sanofi advisory boards; is a member of the speaker's bureau for Miravo, Medexus, Bausch Health, ALK Abello, Sanofi, Pfizer, and Novartis; has received research grants or honoraria for CME events from ALK Abello, Miravo, Medexus, Bausch Health, Sanofi, Pfizer, and Novartis; and is salaried physician at the University of Ottawa. Dr. Kirkpatrick has received an honorarium from Bayer for making an educational podcast on contrast conservation; and is a member of the Provincial CT and MRI committees at the University of Manitoba/Shared Health Services Manitoba. Dr. Copaescu has received research support from the University of Melbourne Research Scholarship and the Montreal General Hospital Foundation; has participated in clinical trials within the past 36 months funded by the Austin Health Foundation; and has presented on media contrast allergy at the American Academy of Allergy, Asthma & Immunology meeting.

Dr. Ling has received an honorarium for medical education speaking engagements from Novartis and Bausch; is on the Board of Directors at the Alberta Medical Association; and is an Assistant Clinical Professor at the University of Alberta. Dr. Ellis has participated on advisory boards for ALK Abello, AstraZeneca, Bausch Health, LEO Pharma, Miravo, Merck, and Novartis; has been a speaker for ALK Abello, AstraZeneca, Bausch, Miravo, Medexus, Mylan, Novartis, Pfizer, Sanofi, StallergenesGreer, and Regeneron; has received research grants from ALK Abello, Aralez, AstraZeneca, Balyer LLC, Medexus, Novartis, Sanofi, and Regeneron; has served as an independent consultant to Bayer LLC, Pharming, and Regeneron; and is the President of the Canadian Society of Allergy and Clinical Immunology.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

D. Blair Macdonald  <https://orcid.org/0000-0003-4526-4504>
 Iain D. C. Kirkpatrick  <https://orcid.org/0000-0001-8951-5016>
 Courtney R. Green  <https://orcid.org/0000-0002-7870-0969>
 Ana Maria Copaescu  <https://orcid.org/0000-0002-9183-5032>
 Matthew D. F. McInnes  <https://orcid.org/0000-0001-8404-4075>
 Andreu F. Costa  <https://orcid.org/0000-0003-1683-8230>

References

1. Macdonald DB, Hurrell C, Costa AF, et al. Canadian Association of Radiologists guidance on contrast associated acute kidney injury. *Can Assoc Radiol J*. 2022;73(3):499-514. doi:10.1177/08465371221083970
2. Schieda N, Blaichman JI, Costa AF, et al. Gadolinium-based contrast agents in kidney disease: comprehensive review and

- clinical practice guideline issued by the Canadian Association of Radiologists. *Can Assoc Radiol J*. 2018;69(2):136-150. doi:10.1016/j.carj.2017.11.002
3. ACR Committee on Drugs and Contrast Media. *ACR Manual on Contrast Media*. American College of Radiology; 2023. Accessed March 29, 2023. https://www.acr.org/-/media/acr/files/clinical-resources/contrast_media.pdf
 4. Sodagari F, Mozaffary A, Wood CG, Schmitz B, Miller FH, Yaghmai V. Reactions to both nonionic iodinated and gadolinium-based contrast media: incidence and clinical characteristics. *Am J Roentgenol*. 2018;210(4):715-719. doi:10.2214/AJR.17.18655
 5. Warrington R, Silviu-Dan F, Wong T. Drug allergy. *Allergy Asthma Clin Immunol*. 2018;14(Suppl 2):60. doi:10.1186/s13223-018-0289-y
 6. Gracia Bara MT, Gallardo-Higueras A, Moreno EM, et al. Hypersensitivity to gadolinium-based contrast media. *Front Allergy*. 2022;3:813927. Accessed October 30, 2023. <https://www.frontiersin.org/articles/10.3389/falgy.2022.813927>
 7. Davenport MS, Weinstein S. (Still) Wondering if we should stop giving steroid preps. *Radiology*. 2021;301(1):141-143. doi:10.1148/radiol.2021211577
 8. Davenport MS, Cohan RH, Ellis JH. Contrast media controversies in 2015: imaging patients with renal impairment or risk of contrast reaction. *AJR Am J Roentgenol*. 2015;204(6):1174-1181. doi:10.2214/AJR.14.14259
 9. Contrast Media Safety Committee. European Society of Urogenital Radiology guidelines on contrast agents. 2018. Accessed May 8, 2023. https://adus-radiologie.ch/files/ESUR_Guidelines_10.0.pdf
 10. Torres MJ, Trautmann A, Böhm I, et al. Practice parameters for diagnosing and managing iodinated contrast media hypersensitivity. *Allergy*. 2021;76(5):1325-1339. doi:10.1111/all.14656
 11. Schabelman E, Witting M. The relationship of radiocontrast, iodine, and seafood allergies: a medical myth exposed. *J Emerg Med*. 2010;39(5):701-707. doi:10.1016/j.jemermed.2009.10.014
 12. Scherer K, Harr T, Bach S, Bircher AJ. The role of iodine in hypersensitivity reactions to radio contrast media. *Clin Exp Allergy*. 2010;40(3):468-475. doi:10.1111/j.1365-2222.2009.03361.x
 13. Caro JJ, Trindade E, McGregor M. The risks of death and of severe nonfatal reactions with high- vs low-osmolality contrast media: a meta-analysis. *AJR Am J Roentgenol*. 1991;156(4):825-832. doi:10.2214/ajr.156.4.1825900
 14. Brockow K. Immediate and delayed cutaneous reactions to radiocontrast media. *Chem Immunol Allergy*. 2012;97:180-190. doi:10.1159/000335631
 15. Brockow K, Romano A, Aberer W, et al. Skin testing in patients with hypersensitivity reactions to iodinated contrast media - a European multicenter study. *Allergy*. 2009;64(2):234-241. doi:10.1111/j.1398-9995.2008.01832.x
 16. Laroche D. Immediate reactions to contrast media: mediator release and value of diagnostic testing. *Toxicology*. 2005;209(2):193-194. doi:10.1016/j.tox.2005.01.010
 17. Mita H, Tadokoro K, Akiyama K. Detection of IgE antibody to a radiocontrast medium. *Allergy*. 1998;53(12):1133-1140. doi:10.1111/j.1398-9995.1998.tb03832.x
 18. Chiu TM, Chu SY. Hypersensitivity reactions to iodinated contrast media. *Biomedicines*. 2022;10(5):1036. doi:10.3390/biomedicines10051036
 19. Cianferoni A. Non-IgE-mediated anaphylaxis. *J Allergy Clin Immunol*. 2021;147(4):1123-1131. doi:10.1016/j.jaci.2021.02.012
 20. Lieberman PL, Seigle RL. Reactions to radiocontrast material. Anaphylactoid events in radiology. *Clin Rev Allergy Immunol*. 1999;17(4):469-496. doi:10.1007/BF02737651
 21. Laroche D, Vergnaud MC, Lefrançois C, Hue S, Bricard H. Anaphylactoid reactions to iodinated contrast media. *Acad Radiol*. 2002;9 Suppl 2:S431-432. doi:10.1016/s1076-6332(03)80253-2
 22. Morcos SK. Review article: acute serious and fatal reactions to contrast media: our current understanding. *Br J Radiol*. 2005;78(932):686-693. doi:10.1259/bjr/26301414
 23. Delgado-Jimenez Y, Perez-Gala S, Aragüés M, Sanchez-Perez J, Garcia-Diez A. Late skin reaction to iodixanol (Visipaque): clinical manifestations, patch test study, and histopathological evaluation. *Contact Dermatitis*. 2006;55(6):348-353. doi:10.1111/j.1600-0536.2006.00957.x
 24. Gómez E, Ariza A, Blanca-López N, Torres MJ. Nonimmediate hypersensitivity reactions to iodinated contrast media. *Curr Opin Allergy Clin Immunol*. 2013;13(4):345-353. doi:10.1097/ACI.0b013e328362b926
 25. An J, Jung H, Kwon OY, et al. Differences in adverse reactions among iodinated contrast media: analysis of the KAERS database. *J Allergy Clin Immunol Pract*. 2019;7(7):2205-2211. doi:10.1016/j.jaip.2019.02.035
 26. Kvedariene V, Orvydaite M, Petraityte P, Rudyte J, Edvardas Tamosiunas A. Inherent clinical properties of non-immediate hypersensitivity to iodinated contrast media. *Int J Clin Pract*. 2021;75(11):e14766. doi:10.1111/ijcp.14766
 27. van der Molen AJ, Dekkers IA, Bediouni I, Darmon-Kern E. A systematic review of the incidence of hypersensitivity reactions and post-contrast acute kidney injury after ioversol in more than 57,000 patients: part 1-intravenous administration. *Eur Radiol*. 2022;32(8):5532-5545. doi:10.1007/s00330-022-08636-3
 28. Peterson A, Katzberg RW, Fung MA, Wootton-Gorges SL, Dager W. Acute generalized exanthematous pustulosis as a delayed dermatotoxic reaction to IV-administered nonionic contrast media. *AJR Am J Roentgenol*. 2006;187(2):W198-W201. doi:10.2214/AJR.05.0317
 29. Hammerbeck AA, Daniels NH, Callen JP. Ioversol-induced acute generalized exanthematous pustulosis: a case report. *Arch Dermatol*. 2009;145(6):683-687. doi:10.1001/archdermatol.2009.100
 30. Poliak N, Elias M, Cianferoni A, Treat J. Acute generalized exanthematous pustulosis: the first pediatric case caused by a contrast agent. *Ann Allergy Asthma Immunol*. 2010;105(3):242-243. doi:10.1016/j.anai.2010.06.018
 31. Machet P, Marcé D, Ziyani Y, et al. Acute generalized exanthematous pustulosis induced by iomeprol with cross-reactivity to other iodinated contrast agents and mild reactions after rechallenge with iopromide and oral corticosteroid premedication. *Contact Dermatitis*. 2019;81(1):74-76. doi:10.1111/cod.13242
 32. Rosado A, Canto G, Veleiro B, Rodríguez J. Toxic epidermal necrolysis after repeated injections of iohexol. *AJR Am J Roentgenol*. 2001;176(1):262-263. doi:10.2214/ajr.176.1.1760262
 33. Laffitte E, Nenadov Beck M, Hofer M, Hohl D, Panizzon RG. Severe Stevens-Johnson syndrome induced by contrast medium iopentol (Imagopaque). *Br J Dermatol*. 2004;150(2):376-378. doi:10.1111/j.1365-2133.2003.05763.x

34. Pop M, Hemenway A, Shakeel F. Probable parenteral and oral contrast-induced Steven Johnson syndrome/toxic epidermal necrolysis. *Am J Emerg Med*. 2021;45:684.e5-684.e6. doi:10.1016/j.ajem.2020.12.044
35. Sullivan CM, Paul NS, Rieder MJ. Bridging the gap between bench and clinic: the importance of understanding the mechanism of iodinated contrast media hypersensitivity. *Br J Radiol*. 2023;96(1141):20220494. doi:10.1259/bjr.20220494
36. McDonald JS, Larson NB, Schmitz JJ, et al. Acute adverse events after iodinated contrast agent administration of 359,977 injections: a single-center retrospective study. *Mayo Clin Proc*. 2023;98(12):1820-1830. doi:10.1016/j.mayocp.2023.02.032
37. Dillman JR, Ellis JH, Cohan RH, Strouse PJ, Jan SC. Frequency and severity of acute allergic-like reactions to gadolinium-containing I.V. contrast media in children and adults. *AJR Am J Roentgenol*. 2007;189(6):1533-1538. doi:10.2214/AJR.07.2554
38. Jung JW, Kang HR, Kim MH, et al. Immediate hypersensitivity reaction to gadolinium-based MR contrast media. *Radiology*. 2012;264(2):414-422. doi:10.1148/radiol.12112025
39. Ramalho J, Semelka RC, Ramalho M, Nunes RH, AlObaidy M, Castillo M. Gadolinium-based contrast agent accumulation and toxicity: an update. *AJNR Am J Neuroradiol*. 2016;37(7):1192-1198. doi:10.3174/ajnr.A4615
40. Ahn YH, Kang DY, Park SB, et al. Allergic-like hypersensitivity reactions to gadolinium-based contrast agents: an 8-year cohort study of 154 539 patients. *Radiology*. 2022;303(2):329-336. doi:10.1148/radiol.210545
41. Behzadi AH, Zhao Y, Farooq Z, Prince MR. Immediate allergic reactions to gadolinium-based contrast agents: a systematic review and meta-analysis. *Radiology*. 2018;286(2):471-482. doi:10.1148/radiol.2017162740
42. Prince MR, Zhang H, Zou Z, Staron RB, Brill PW. Incidence of immediate gadolinium contrast media reactions. *AJR Am J Roentgenol*. 2011;196(2):W138-W143. doi:10.2214/AJR.10.4885
43. Power S, Talbot N, Kucharczyk W, Mandell DM. Allergic-like reactions to the MR imaging contrast agent gadobutrol: a prospective study of 32 991 consecutive injections. *Radiology*. 2016;281(1):72-77. doi:10.1148/radiol.2016151066
44. Lee SY, Lim KW, Chang YS. Radiocontrast media hypersensitivity in the Asia Pacific region. *Asia Pac Allergy*. 2014;4(2):119-125. doi:10.5415/apallergy.2014.4.2.119
45. Li X, Liu H, Zhao L, et al. Clinical observation of adverse drug reactions to non-ionic iodinated contrast media in population with underlying diseases and risk factors. *Br J Radiol*. 2017;90(1070):20160729. doi:10.1259/bjr.20160729
46. Voltolini S, Cofini V, Murzilli F, et al. Hypersensitivity reactions to iodinate contrast media in Italy: a retrospective study. Characteristics of patients and risk factors. *Eur Ann Allergy Clin Immunol*. 2022;54(2):60-67. doi:10.23822/EurAnnACI.1764-1489.225
47. Cha MJ, Kang DY, Lee W, et al. Hypersensitivity reactions to iodinated contrast media: a multicenter study of 196 081 patients. *Radiology*. 2019;293(1):117-124. doi:10.1148/radiol.2019190485
48. Nelson KL, Gifford LM, Lauber-Huber C, Gross CA, Lasser TA. Clinical safety of gadopentetate dimeglumine. *Radiology*. 1995;196(2):439-443. doi:10.1148/radiology.196.2.7617858
49. Granata V, Cascella M, Fusco R, et al. Immediate adverse reactions to gadolinium-based MR contrast media: a retrospective analysis on 10,608 examinations. *BioMed Res Int*. 2016;2016:3918292. doi:10.1155/2016/3918292
50. Heshmatzadeh Behzadi A, Prince MR. Preventing allergic reactions to gadolinium-based contrast agents. *Top Magn Reson Imaging*. 2016;25(6):275-279. doi:10.1097/RMR.0000000000000106
51. Ryoo CH, Choi YH, Cheon JE, et al. Preventive effect of changing contrast media in patients with a prior mild immediate hypersensitivity reaction to gadolinium-based contrast agent. *Invest Radiol*. 2019;54(10):633-637. doi:10.1097/RLI.0000000000000573
52. Nyman U, Ekberg O, Aspelin P. Torsten Almén (1931-2016): the father of non-ionic iodine contrast media. *Acta Radiol Stockh Swed* 1987. 2016;57(9):1072-1078. doi:10.1177/0284185116648504
53. Greenberger PA, Patterson R, Simon R, Lieberman P, Wallace W. Pretreatment of high-risk patients requiring radiographic contrast media studies. *J Allergy Clin Immunol*. 1981;67(3):185-187. doi:10.1016/0091-6749(81)90059-2
54. Lasser EC, Berry CC, Talner LB, et al. Pretreatment with corticosteroids to alleviate reactions to intravenous contrast material. *N Engl J Med*. 1987;317(14):845-849. doi:10.1056/NEJM198710013171401
55. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. *Radiology*. 1990;175(3):621-628. doi:10.1148/radiology.175.3.2343107
56. Greenberger PA, Patterson R. The prevention of immediate generalized reactions to radiocontrast media in high-risk patients. *J Allergy Clin Immunol*. 1991;87(4):867-872. doi:10.1016/0091-6749(91)90135-b
57. 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(3):523-526. doi:10.2214/ajr.162.3.8109489
58. Lee SY, Yang MS, Choi YH, et al. Stratified premedication strategy for the prevention of contrast media hypersensitivity in high-risk patients. *Ann Allergy Asthma Immunol*. 2017;118(3):339-344.e1. doi:10.1016/j.anai.2016.11.027
59. Park SJ, Kang DY, Sohn KH, et al. Immediate mild reactions to CT with iodinated contrast media: strategy of contrast media readministration without corticosteroids. *Radiology*. 2018;288(3):710-716. doi:10.1148/radiol.2018172524
60. Kolbe AB, Hartman RP, Hoskin TL, et al. Premedication of patients for prior urticarial reaction to iodinated contrast medium. *Abdom Imaging*. 2014;39(2):432-437. doi:10.1007/s00261-013-0058-9
61. McDonald JS, Larson NB, Kolbe AB, et al. Prevention of allergic-like reactions at repeat CT: steroid pretreatment versus contrast material substitution. *Radiology*. 2021;301(1):133-140. doi:10.1148/radiol.2021210490
62. Davenport MS, Cohan RH. The evidence for and against corticosteroid prophylaxis in at-risk patients. *Radiol Clin North Am*. 2017;55(2):413-421. doi:10.1016/j.rcl.2016.10.012
63. Sheikh A. Glucocorticosteroids for the treatment and prevention of anaphylaxis. *Curr Opin Allergy Clin Immunol*. 2013;13(3):263-267. doi:10.1097/ACI.0b013e32832836097f4
64. Shaker MS, Wallace DV, Golden DBK, 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(4):1082-1123. doi:10.1016/j.jaci.2020.01.017
65. Mervak BM, Davenport MS, Ellis JH, Cohan RH. Rates of breakthrough reactions in inpatients at high risk receiving pre-medication before contrast-enhanced CT. *AJR Am J Roentgenol.* 2015;205(1):77-84. doi:10.2214/AJR.14.13810
 66. Freed KS, Leder RA, Alexander C, DeLong DM, Kliever MA. Breakthrough adverse reactions to low-osmolar contrast media after steroid premedication. *AJR Am J Roentgenol.* 2001;176(6):1389-1392. doi:10.2214/ajr.176.6.1761389
 67. Park HJ, Park JW, Yang MS, 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(7):2886-2893. doi:10.1007/s00330-016-4682-y
 68. Yocum MW, Butterfield JH, Klein JS, Volcheck GW, Schroeder DR, Silverstein MD. Epidemiology of anaphylaxis in Olmsted County: a population-based study. *J Allergy Clin Immunol.* 1999;104(2):452-456. doi:10.1016/S0091-6749(99)70392-1
 69. 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(2):492-501. doi:10.1148/radiol.2015151143
 70. Waljee AK, Rogers MAM, Lin P, 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. doi:10.1136/bmj.j1415
 71. Dilisio MF. Osteonecrosis following short-term, low-dose oral corticosteroids: a population-based study of 24 million patients. *Orthopedics.* 2014;37(7):e631-636. doi:10.3928/01477447-20140626-54
 72. Gray N, Howard A, Zhu J, Feldman LY, To T. Association between inhaled corticosteroid use and bone fracture in children with asthma. *JAMA Pediatr.* 2018;172(1):57-64. doi:10.1001/jamapediatrics.2017.3579
 73. Mervak BM, Cohan RH, Ellis JH, Khalatbari S, Davenport MS. Intravenous corticosteroid premedication administered 5 hours before CT compared with a traditional 13-hour oral regimen. *Radiology.* 2017;285(2):425-433. doi:10.1148/radiol.2017170107
 74. Greenberger PA, Halwig JM, Patterson R, Wallemark CB. Emergency administration of radiocontrast media in high-risk patients. *J Allergy Clin Immunol.* 1986;77(4):630-634. doi:10.1016/0091-6749(86)90357-x
 75. Abe S, Fukuda H, Tobe K, Ibukuro K. Protective effect against repeat adverse reactions to iodinated contrast medium: pre-medication vs. changing the contrast medium. *Eur Radiol.* 2016;26(7):2148-2154. doi:10.1007/s00330-015-4028-1
 76. Umakoshi H, Nihashi T, Takada A, et al. Iodinated contrast media substitution to prevent recurrent hypersensitivity reactions: a systematic review and meta-analysis. *Radiology.* 2022;305(2):341-349. doi:10.1148/radiol.220370
 77. Kim S, Jeon KN, Jung JW, et al. Substitution with low-osmolar iodinated contrast agent to minimize recurrent immediate hypersensitivity reaction. *Radiology.* 2023;309(1):e222467. doi:10.1148/radiol.222467
 78. Sohn KH, Seo JH, Kang DY, Lee SY, Kang HR. Finding the optimal alternative for immediate hypersensitivity to low-osmolar iodinated contrast. *Invest Radiol.* 2021;56(8):480-485. doi:10.1097/RLI.0000000000000765
 79. Murphy KP, Szopinski KT, Cohan RH, Mermillod B, Ellis JH. Occurrence of adverse reactions to gadolinium-based contrast material and management of patients at increased risk: a survey of the American Society of Neuroradiology Fellowship Directors. *Acad Radiol.* 1999;6(11):656-664. doi:10.1016/S1076-6332(99)80114-7
 80. Schieda N, Maralani PJ, Hurrell C, Tsampalieros AK, Hiremath S. Updated clinical practice guideline on use of gadolinium-based contrast agents in kidney disease issued by the Canadian Association of Radiologists. *Can Assoc Radiol J.* 2019;70(3):226-232. doi:10.1016/j.carj.2019.04.001
 81. 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(2):312-321. doi:10.1148/radiol.2020192855
 82. 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(6):369-373. doi:10.1097/RLI.0000000000000750
 83. The Royal Australian and New Zealand College of Radiologists. *Iodinated Contrast Media Guideline.* RANZCR; 2018. Accessed April 29, 2024. <https://www.ranzcr.com/college/document-library/iodinated-contrast-guidelines-2016>
 84. The Royal College of Radiologists. Guidance on gadolinium-based contrast agent administration to adult patients. 2019. Accessed May 16, 2024. <https://www.rcr.ac.uk/our-services/all-our-publications/clinical-radiology-publications/guidance-on-gadolinium-based-contrast-agent-administration-to-adult-patients/>
 85. Kang HR, Jeong J, Brockow K. Diagnosis and prevention of hypersensitivity reactions to iodinated contrast media. *Allergy Asthma Immunol Res.* 2022;14(4):348-360. doi:10.4168/aair.2022.14.4.348
 86. Kim JH, Choi SI, Lee YJ, et al. Pharmacological prevention of delayed hypersensitivity reactions caused by iodinated contrast media. *World Allergy Organ J.* 2021;14(7):100561. doi:10.1016/j.waojou.2021.100561
 87. Kang DY, Lee SY, Ahn YH, et al. Incidence and risk factors of late adverse reactions to low-osmolar contrast media: a prospective observational study of 10,540 exposures. *Eur J Radiol.* 2022;146:110101. doi:10.1016/j.ejrad.2021.110101
 88. Davis PL. Anaphylactoid reactions to the nonvascular administration of water-soluble iodinated contrast media. *AJR Am J Roentgenol.* 2015;204(6):1140-1145. doi:10.2214/AJR.15.14507
 89. Endrikat J, Chernova J, Gerlinger C, et al. Risk of hypersensitivity reactions to iopromide in children and elderly: an analysis of 132,850 patients from 4 observational studies and pharmacovigilance covering >288 million administrations. *Invest Radiol.* 2022;57(5):318. doi:10.1097/RLI.0000000000000840
 90. Trout AT, Dillman JR, Ellis JH, Cohan RH, Strouse PJ. Patterns of intravenous contrast material use and corticosteroid premedication in children—a survey of Society of Chairs of Radiology in Children's Hospitals (SCORCH) member institutions. *Pediatr Radiol.* 2011;41(10):1272-1283. doi:10.1007/s00247-011-2112-5
 91. Aljebab F, Choonara I, Conroy S. Systematic review of the toxicity of short-course oral corticosteroids in children.

- Arch Dis Child.* 2016;101(4):365-370. doi:10.1136/archdis-child-2015-309522
92. Deng F, Li MD, Wong A, et al. Quality of documentation of contrast agent allergies in electronic health records. *J Am Coll Radiol.* 2019;16(8):1027-1035. doi:10.1016/j.jacr.2019.01.027
 93. Boukantar M, Chiaroni PM, Gallet R, et al. A randomized controlled trial of nonfasting vs fasting before interventional coronary procedures: the TONIC trial. *JACC Cardiovasc Interv.* 2024;17(10):1200-1210. doi:10.1016/j.jcin.2024.03.033
 94. Neeman Z, Abu Ata M, Touma E, et al. Is fasting still necessary prior to contrast-enhanced computed tomography? A randomized clinical study. *Eur Radiol.* 2021;31(3):1451-1459. doi:10.1007/s00330-020-07255-0
 95. Barbosa PNVP, Bitencourt AGV, Tyng CJ, et al. JOURNAL CLUB: preparative fasting for contrast-enhanced CT in a cancer center: a new approach. *AJR Am J Roentgenol.* 2018;210(5):941-947. doi:10.2214/AJR.17.19061
 96. Lee BY, Ok JJ, Abdelaziz Elsayed AA, Kim Y, Han DH. Preparative fasting for contrast-enhanced CT: reconsideration. *Radiology.* 2012;263(2):444-450. doi:10.1148/radiol.12111605
 97. Yoon SH, Lee SY, Kang HR, et al. Skin tests in patients with hypersensitivity reaction to iodinated contrast media: a meta-analysis. *Allergy.* 2015;70(6):625-637. doi:10.1111/all.12589
 98. Bansie RD, Karim AF, van Maaren MS, et al. Assessment of immediate and non-immediate hypersensitivity contrast reactions by skin tests and provocation tests: a review. *Int J Immunopathol Pharmacol.* 2021;35:20587384211015061. doi:10.1177/20587384211015061
 99. Lee JH, Kwon OY, Park SY, et al. Validation of the pre-screening intradermal skin test for predicting hypersensitivity to iodinated contrast media: a prospective study with ICM challenge. *J Allergy Clin Immunol Pract.* 2020;8(1):267-272. doi:10.1016/j.jaip.2019.08.001
 100. Soyyigit S, Goksel O, Aydin O, Gencturk Z, Bavbek S. What is the clinical value of negative predictive values of skin tests to iodinated contrast media? *Allergy Asthma Proc.* 2016;37(6):482-488. doi:10.2500/aap.2016.37.4000
 101. 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(4):1246-1254. doi:10.1016/j.jaip.2017.10.040
 102. Doña I, Bogas G, Salas M, et al. Hypersensitivity reactions to multiple iodinated contrast media. *Front Pharmacol.* 2020;11:575437. doi:10.3389/fphar.2020.575437
 103. Caimmi S, Benyahia B, Suau D, et al. Clinical value of negative skin tests to iodinated contrast media. *Clin Exp Allergy.* 2010;40(5):805-810. doi:10.1111/j.1365-2222.2010.03493.x
 104. Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol.* 2010;105(4):259-273. doi:10.1016/j.anai.2010.08.002
 105. Ahn KM, Ahn YH, Cho MK, Kang DY, Lee SY, Kang HR. Validation of practical pathway in patients with anaphylaxis to low osmolar contrast media: a retrospective cohort study. *J Allergy Clin Immunol Pract.* 2022;10(10):2685-2692.e2. doi:10.1016/j.jaip.2022.03.030
 106. Fein MN, Fischer DA, O'Keefe AW, Sussman GL. CSACI position statement: newer generation H1-antihistamines are safer than first-generation H1-antihistamines and should be the first-line antihistamines for the treatment of allergic rhinitis and urticaria. *Allergy Asthma Clin Immunol.* 2019;15(1):1-6. doi:10.1186/s13223-019-0375-9
 107. Schwartz LB, Yunginger JW, Miller J, Bokhari R, Dull D. Time course of appearance and disappearance of human mast cell tryptase in the circulation after anaphylaxis. *J Clin Invest.* 1989;83(5):1551-1555. doi:10.1172/JCI114051
 108. Sala-Cunill A, Cardona V, Labrador-Horrillo M, et al. Usefulness and limitations of sequential serum tryptase for the diagnosis of anaphylaxis in 102 patients. *Int Arch Allergy Immunol.* 2013;160(2):192-199. doi:10.1159/000339749
 109. Oosting E, Keyzer JJ, Wolthers BG. Correlation between urinary levels of histamine metabolites in 24-hour urine and morning urine samples of man: influence of histamine-rich food. *Agents Actions.* 1989;27(1-2):205-207. doi:10.1007/BF02222240
 110. Hogan AD, Schwartz LB. Markers of mast cell degranulation. *Methods.* 1997;13(1):43-52. doi:10.1006/meth.1997.0494
 111. van Doormaal JJ, van der Veer E, van Voorst Vader PC, et al. Tryptase and histamine metabolites as diagnostic indicators of indolent systemic mastocytosis without skin lesions. *Allergy.* 2012;67(5):683-690. doi:10.1111/j.1398-9995.2012.02809.x
 112. Tomasiak-Łozowska MM, Klimek M, Lis A, Moniuszko M, Bodzenta-Lukaszyk A. Markers of anaphylaxis - a systematic review. *Adv Med Sci.* 2018;63(2):265-277. doi:10.1016/j.advms.2017.12.003
 113. Lin RY, Schwartz LB, Curry A, et al. Histamine and tryptase levels in patients with acute allergic reactions: an emergency department-based study. *J Allergy Clin Immunol.* 2000;106(1 Pt 1):65-71. doi:10.1067/mai.2000.107600
 114. Pinnobphun P, Buranapraditkun S, Kampitak T, Hirankarn N, Klaewsongkram J. The diagnostic value of basophil activation test in patients with an immediate hypersensitivity reaction to radiocontrast media. *Ann Allergy Asthma Immunol.* 2011;106(5):387-393. doi:10.1016/j.anai.2010.12.020