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GUIDELINES AND POSITION STATEMENTS

Philippine Journal of Allergy, Asthma and Immunology

Position Statements of The Philippine Society of Allergy, Asthma and Immunology on Risk Assessment and Preventive Strategies for Hypersensitivity Reactions to Radiocontrast Media*

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Keywords: contrast media, drug hypersensitivity, anaphylaxis, premedication, skin tests, risk assessment

*These Position Statements were developed and adopted by the Drug Allergy Council of the Philippine Journal of Allergy, Asthma and Immunology (PJAAI) on September 6, 2026. The Council members are listed above, with Dr. Maria Carmen D. Ang serving as Chair.

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KEY POSITION STATEMENTS

Statement 1: Risk Stratification and Indications for Testing / Premedication

- The strongest and most consistent risk factor for both immediate and non-immediate hypersensitivity reactions is a history of a previous hypersensitivity reaction to radiocontrast media (RCM).
- For all patients with a previous hypersensitivity reaction to a RCM, consider an un-enhanced examination or an alternative imaging modality when it can provide sufficient diagnostic information for appropriate patient management. However, a clinically indicated contrast-enhanced examination should not be withheld when no suitable alternative imaging strategy is available.
- Premedication and diagnostic testing should not be performed solely on the basis of the following:
    - isolated risk factors, which include unrelated drug allergies, food allergy (e.g., seafood allergy), stinging insect allergy, family history of hypersensitivity reactions to RCM, female sex, asthma, use of beta-blockers or angiotensin-converting enzyme (ACE) inhibitors and underlying cardiovascular disease.
    - physiologic (non-hypersensitivity) reactions (e.g., warmth, flushing, nausea, vasovagal responses) to RCM.
- Routine corticosteroid and/or antihistamine premedication must not be used as a substitute for selecting an alternative RCM.

Statement 2: Role of Diagnostic Testing (Skin Testing & Drug Provocation Testing)

- In patients with a history of immediate or non-immediate (maculopapular exanthem) hypersensitivity reaction to Iodinated Contrast Media (ICM), or Gadolinium Based Contrast Agent (GBCA) scheduled for elective or non-urgent contrast imaging, diagnostic evaluation by a board-certified allergist may be performed to select a potentially safer alternative agent.
- Skin testing (skin prick test or SPT/intradermal test or IDT) for immediate hypersensitivity reactions (IHR) is best performed 2–6 months after the reaction, when sensitivity is highest. The sensitivity of the test is lower when it is performed within the first month or more than 12 months after the reaction. For non-immediate hypersensitivity reactions (NIHR), IDT with delayed reading may be considered, preferably performed more than 6 months after the reaction. A negative skin test reduces but does not completely exclude the likelihood of hypersensitivity.
- After a negative skin test, a supervised drug provocation test (DPT) or graded challenge may be considered to confirm tolerance to an alternative RCM. A negative DPT supports agent-specific tolerance under the tested conditions; however, it does not guarantee immunity against reactions to future exposures or to other RCMs.
- In patients with non-immediate hypersensitivity reactions presenting as severe cutaneous adverse reactions (SCARs) – including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), and Acute Generalized Exanthematous Pustulosis (AGEP)—to prevent the risk of re-inducing SCAR, strict avoidance of in vivo diagnostic tests (SPT/IDT/DPT) is recommended to all ICM classes if the reaction was due to an ICM and to all groups of GBCA if the reaction was due to a GBCA.

Statement 3: Preventive strategies in Mild Immediate Hypersensitivity Reactions (IHR)

- Referral to a board-certified allergist may be considered if the patient has not been previously evaluated.
- If the culprit is known, switch to an alternative RCM belonging to a different group based on cross-reactivity.
- If the culprit ICM is unknown, select an ICM from Group B or Group D, since the culprit agent is most likely from Group A. The ICMs in Groups A and C have a high likelihood of cross-reactivity and should therefore be avoided whenever possible (Tables 1 and 5).
- If the culprit GBCA is unknown, select a GBCA different from the one routinely administered (Table 5).
- **Premedication is not necessary** for mild IHR particularly when an appropriate alternative RCM can be selected.
- Observe the patient for at least 30 minutes after RCM administration and remain vigilant for recurrent IHR. If an IHR occurs, it is recommended to treat promptly and refer to a board-certified allergist.

Statement 4: Preventive Strategies in Moderate Immediate Hypersensitivity Reactions

- Referral to a board-certified allergist may be considered if the patient has not been previously evaluated.
- For urgent or emergency imaging:
    - If the culprit is known, switch to an alternative RCM belonging to a different group based on cross-reactivity.
    - If the culprit ICM is unknown, select an ICM from Group B or Group D, since the culprit agent is most likely from Group A. The ICMs in Groups A and C have a high likelihood of cross-reactivity and should therefore be avoided whenever possible (Tables 1 and 5).
    - If the culprit GBCA is unknown, select a GBCA different from the one routinely administered (Table 5).

- Premedication remains an option for exceptional circumstances (e.g., urgent imaging when the culprit agent is unknown or if an alternative agent is not available for testing, in high-risk patients with multiple co-morbidities), although supporting evidence is of low certainty.
- Ensure that a trained imaging or emergency physician is readily available.

- For non-urgent or elective imaging:
  - Postpone the procedure until the allergy evaluation is completed, and an alternative ICM or GBCA is recommended by an allergist.
- Observe the patient for at least 30 minutes after RCM administration and remain vigilant for recurrent IHR. If an IHR occurs, it is recommended to treat promptly and refer to a board-certified allergist.

Statement 5: Preventive Strategies in Severe Immediate Reactions and Anaphylaxis

- Perform a **non-contrast imaging or an alternative imaging modality** if feasible.
- Referral to a board-certified allergist may be considered if the patient has not been previously evaluated.
- For urgent or emergency imaging:
  - If the culprit is known, switch to an alternative RCM belonging to a different group based on cross-reactivity.
  - If the culprit ICM is unknown, select an ICM from Group B or Group D, since the culprit agent is most likely from Group A. The ICMs in Groups A and C have a high likelihood of cross-reactivity and should therefore be avoided whenever possible (Tables 1 and 5).
  - If the culprit GBCA is unknown, select a GBCA different from the one routinely administered (Table 5).
  - Ensure that a trained imaging or emergency physician is readily available.
- For non-urgent or elective imaging:
  - Postpone the procedure until the allergy evaluation is completed, and an alternative ICM or GBCA is recommended by an allergist.
- If an alternative RCM is not available, a multidisciplinary discussion is recommended before deciding to proceed with the RCM administration, in a setting where advanced resuscitation is immediately available. The selection of a specific alternative RCM must be done in consultation with allergy/immunology and radiology.
- **Administer premedication** while recognizing that it does not fully prevent breakthrough hypersensitivity reactions.
- Observe the patient for at least 30 minutes after RCM administration and remain vigilant for recurrent IHR. If an IHR occurs, it is recommended to treat promptly and refer to a board-certified allergist.

Statement 6: Preventive Strategies in Non-immediate Hypersensitivity Reaction (NIHR) presenting as Maculopapular Exanthem (MPE)

- Refer the patient to a board-certified allergist if not previously evaluated.
- If the culprit is known, switch to an alternative RCM belonging to a different group based on cross-reactivity.
- If the culprit ICM is unknown, select an ICM from Group B or Group D, since the culprit agent is most likely from Group A. The ICMs in Groups A and C have a high likelihood of cross-reactivity and should therefore be avoided whenever possible. (Tables 1 and 5).
- If the culprit GBCA is unknown, select a GBCA different from the one routinely administered (Table 5).
- **Premedication is not supported by current evidence** for preventing non-immediate hypersensitivity reactions.
- Observe the patient for at least 30 minutes after RCM administration and remain vigilant for recurrent NIHR in the next few days. If an NIHR occurs, it is recommended to treat promptly and refer to a board-certified allergist.

Statement 7: Preventive Strategies in Severe Cutaneous Adverse Reactions (SCARs)

- Referral to a board-certified allergist may be considered if the patient has not been previously evaluated.
- Perform a **non-contrast imaging** or an **alternative imaging modality** whenever feasible to avoid re-exposure to the culprit RCM and other agents of the same type (i.e., if an ICM is the culprit, avoid all ICM; if a GBCA is the culprit, avoid all GBCA).

Statement 8: Patient Labeling and Medical Record Documentation

- Patients with prior hypersensitivity reactions to RCM should not be broadly labeled as having a generic "radiocontrast media allergy," "dye allergy," "iodine allergy," or "gadolinium allergy".
  - **Medical Records:** Detailed medical records must include the specific contrast agent (brand/trade name and generic name), date and type of reaction, severity, treatment administered and outcome.
  - **Documentation of Tolerance:** Agents that were tolerated during supervised DPT after a negative skin test or subsequent uneventful contrast-enhanced procedures should be documented specifically as **agent-specific tolerance**, rather than as blanket tolerance to all contrast agents or blanket avoidance of future contrast agents.

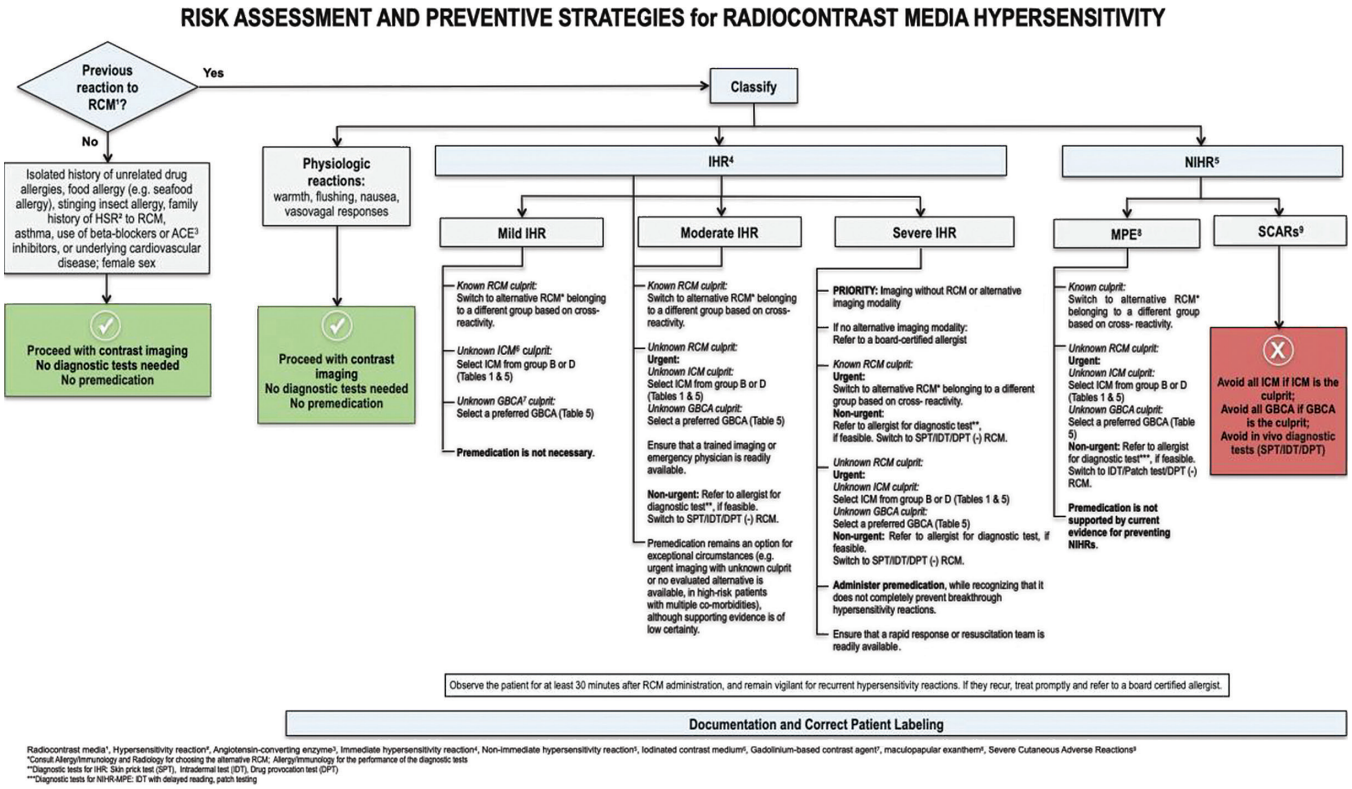


Figure 1. Algorithm on the risk assessment and preventive strategies for radiocontrast hypersensitivity.

INTRODUCTION

Hypersensitivity reactions to radiocontrast media (RCM) are increasingly encountered due to the growing number of diseases requiring contrast-enhanced diagnostic imaging. Advances in imaging technology have further expanded the use of RCM across a wide range of clinical settings. Physicians are encountering more scenarios that require the most appropriate strategies to minimize the risk of recurrent hypersensitivity reactions in patients with prior history of RCM hypersensitivity. These strategies may include skin testing, drug provocation test or graded drug challenge, selection of an alternative contrast agent, and premedication, depending on the clinical scenario.

In the Philippines, there are currently no locally developed, standardized guidelines to assist physicians in the risk assessment and preventive strategies for patients with a history of hypersensitivity reactions to RCM. These position statements were therefore developed to provide evidence-based, practical recommendations that are applicable within the local healthcare setting (Figure 1). It aims to guide clinicians in selecting appropriate diagnostic and preventive measures based on available resources, thereby promoting consistent clinical practice, enhancing physician confidence in decision-making, and ultimately improving patient safety.

METHODOLOGY

This document was the initiative of the Drug Allergy Council of the Philippine Society of Allergy, Asthma and Immunology (PSAAI). The group is comprised of specialists in either internal medicine or pediatrics who are board-certified allergists/immunologists. These position statements were developed through detailed literature review on the current best available evidence and group consensus meetings.

RADIOCONTRAST MEDIA (RCM)

Radiocontrast media are substances used in medical imaging techniques such as X-ray contrast imaging, computed tomography (CT), and magnetic resonance imaging (MRI) to improve the visibility of internal structures. They enhance image quality by increasing the radiodensity of specific tissues, enabling clearer distinction from adjacent anatomy. These agents play a crucial role in modern diagnostic imaging by highlighting internal organs/structures, vascular abnormalities, tumors, and inflammatory conditions.[1]

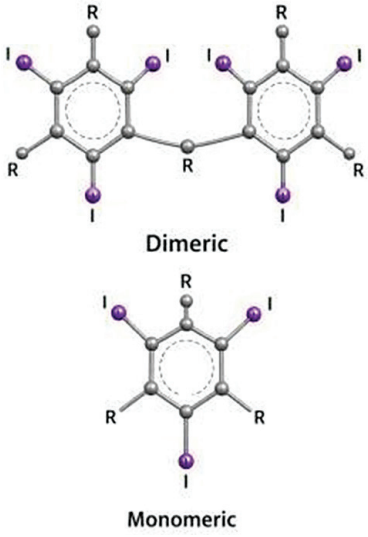


Figure 2. Simplified structure of monomeric and dimeric iodinated contrast media. *Adapted from.*[51]

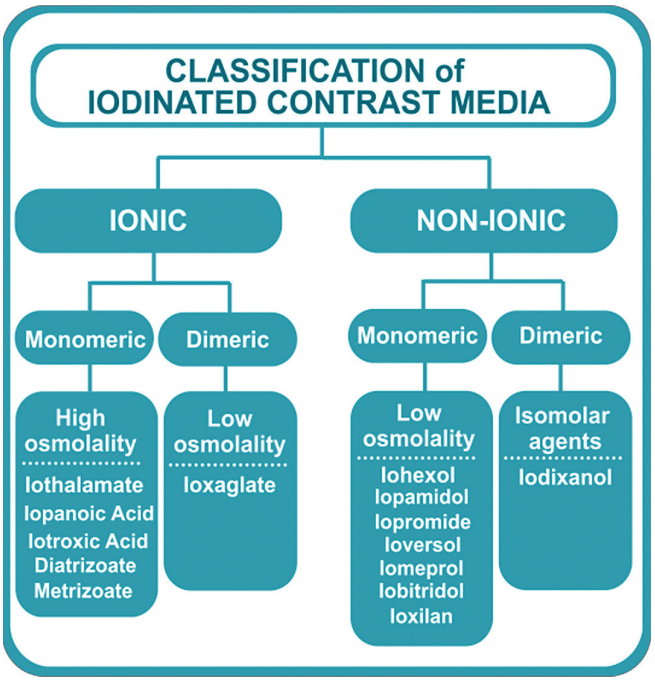


Figure 3. Classification of iodinated contrast media. *Adapted from Rosado Ingelmo et al.*[2]

Types of radiocontrast media:

- Iodinated contrast media
- Barium sulfate
- Gadolinium-based contrast agents

***Iodinated contrast media* (ICM)** are widely used in radiographic imaging and computed tomography (CT) to enhance the visualization of internal organs and vascular anatomy. Although intravenous (IV) administration is the most common route, ICM may also be administered via intra-arterial (IA), intrathecal (IT), enteral (oral or rectal), and direct or specialized routes, including intra-articular, retrograde urologic, and biliary duct administration, depending on the clinical indication. Chemically, ICMs are iodine-containing organic compounds based on a triiodinated benzene ring, consisting of a benzene ring with three covalently bound iodine atoms. They are broadly classified as ionic or non-ionic according to their chemical structure and behavior in aqueous solution, specifically whether they dissociate into ions. Ionic ICMs dissociate into ions or charged particles in solution, whereas non-ionic ICMs do not dissociate into ions. They may exist as monomers, containing a single benzene ring, or as dimers, in which two benzoic nuclei are covalently linked (Figure 2).[2]

ICM are classified into four groups based on ionicity and the number of triiodinated benzene rings (Figure 3):[2,3]

1. Ionic monomers contain a single negatively charged triiodinated benzene ring paired with sodium and/or meglumine as a counter-ion. These agents have the highest osmolality (>1400 mOsm/kg H_2O), approximately five to seven times that of normal human serum, and are therefore classified as hypertonic or high-osmolar contrast media.
2. Ionic dimers consist of two triiodobenzene rings containing a carboxyl group. They exhibit lower osmolality (~600 mOsm/kg H_2O), about two to three times that of normal human serum, and are considered low-osmolar or hypotonic contrast agents.
3. Non-ionic monomers are triiodinated compounds with hydrophilic hydroxyl side chains. These agents have osmolality ranging from 500 to 850 mOsm/kg H_2O, also approximately two to three times that of normal human serum, and are classified as low-osmolar or hypotonic ICM.
4. Non-ionic dimers contain two non-ionic triiodinated benzene rings and demonstrate the lowest osmolality among ICM (~290 mOsm/kg H_2O), closely approximating that of human serum. As such, they are considered isotonic or iso-osmolar contrast media.

Hypersensitivity reactions (HSRs) have been documented with the use of ICM. In a large multicenter study involving 196,081 patients, the overall incidence of ICM-associated

HSRs was 0.73%, with severe reactions occurring in 0.01% of cases.[4] The immunogenicity of ICM is largely determined by their chemical characteristics, including iodine content, aromatic ring structures, side-chain composition, ionicity, osmolality, molecular configuration (monomeric or dimeric), hydrophilicity or lipophilicity, and surface charge. The reaction may be directed against the benzene ring to which the iodine atoms are attached, rather than against the iodine ion itself.[5]

Cross-reactivity among ICM has been well documented. Contrary to common misconceptions, iodine itself is not responsible for cross-reactivity;[6] rather, it is the shared molecular structures of RCM that determine antigenic similarity. Cross-reactivity is frequently associated with common side chains, particularly the N-(2,3-dihydroxypropyl) carbamoyl group, which may serve as an antigenic determinant.[7] Observational studies have shown that switching to an alternative ICM with a different side chain can reduce the risk of recurrent hypersensitivity reactions by up to 61% in patients with a history of ICM-induced HSR.[8]

A recent paper by Vega F et al proposed the classification of ICM into four groups based on patterns of clinical cross-reactivity to guide the selection of safer alternatives (Table 1):[7]

- Group A (High cross-reactivity): Includes iodixanol, iomeprol, iohexol, and ioversol, all of which share the classic N-(2,3-dihydroxypropyl) carbamoyl side chain.
- Group B: Includes iopamidol formulated with two 1-N,3-N-bis(1,3-dihydroxypropan-2-yl) side chains.
- Group C: Includes iopromide, which exhibits mixed structural features, containing both classic and modified carbamoyl side chains.
- Group D: (Distinct molecular structure): Includes iobitridol, characterized by a modified carbamoyl side chain, N-(2,3-dihydroxypropyl)-N-methyl-carbamoyl (Table 1).

ICM formulations contain various excipients. Sodium calcium edetate is present in both ionic and non-ionic ICM, while tromethamine (also known as trometamol or tris) is included in several monomeric and dimeric non-ionic ICM preparations. These excipients may contribute to the development of hypersensitivity reactions associated with ICM use (Table 2).[3]

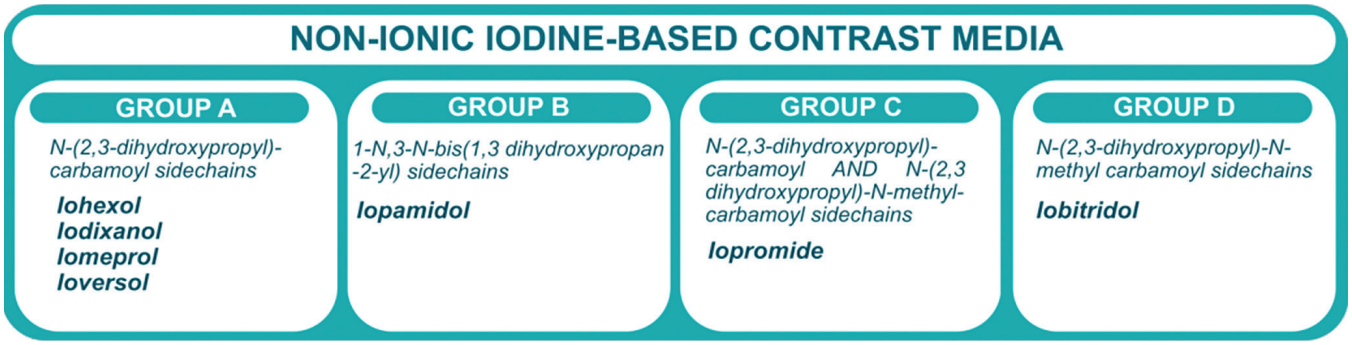
Barium sulfate ($BaSO_4$) is an inorganic, odorless, white crystalline compound that is insoluble in water. It is commonly used as a contrast agent in medical imaging, particularly for gastrointestinal (GI) tract examinations. When administered orally or as an enema, barium sulfate coats the mucosal surfaces of the esophagus, stomach, and intestines, thereby enhancing their visualization on X-ray and computed tomography (CT) imaging.[9]

Although barium sulfate itself is generally considered safe, hypersensitivity reactions are more frequently attributed to the excipients rather than to the active compound.[10] These include emulsifiers, stabilizers, and dispersants—such as carboxymethylcellulose sodium, sodium citrate, simethicone, and polysorbate 80—which help maintain uniform suspension of $BaSO_4$ particles in water. Additional components include mucosal-coating and non-coating thickeners (e.g., acacia gum, tragacanth gum, xanthan gum, carrageenan, pectin, modified corn starch, and methylcellulose), sweeteners, texturizers, and laxatives (e.g., glycerin, maltodextrin, xylitol, and sorbitol), as well as preservatives such as sodium benzoate, potassium sorbate, methylparaben, and propylparaben.[11]

It is important to note that barium sulfate is chemically unrelated to sulfonamide ("sulfa") drugs; therefore, a history of sulfa drug allergy does not inherently increase the risk of a hypersensitivity reaction to barium sulfate (Atlantic Medical Imaging, n.d.).

Gadolinium-based contrast agents (GBCAs) are widely used in radiology to enhance the sensitivity and specificity of magnetic resonance imaging (MRI) examinations and

Table 1. Classification of iodinated contrast media into groups based on patterns of clinical cross-reactivity. *Adapted from Vega et al.*[7]



are primarily administered via IV route. Because free gadolinium is inherently toxic, all GBCAs incorporate a chelating agent—either linear or macrocyclic in structure—that binds the gadolinium ion, thereby improving its stability, solubility, and safety. Accordingly, GBCAs are classified as linear or macrocyclic based on the structure of the organic ligand, and as ionic or non-ionic according to their net charge in solution (Figure 4).[7,12]

Most commonly used GBCAs are extracellular agents that are predominantly eliminated via the kidneys, although limited hepatic excretion has been demonstrated for certain

Table 2. Types of iodinated contrast media and their characteristics. *Adapted from Chiu and Chu*[3]

GENERIC NAME	TRADE NAME	IONIC/ NON-IONIC	MONOMER/ DIMER	IODINE CONTENT (mg/mL)	OSMOLALITY (mOsm/kg H_2O	OSMOLAR	Excipients with Reported Hypersensitivity
Iothalamate	Conray	Ionic	Monomer	325	1843	High	Sodium calcium edatate
Amidotrizoate	Urografin 76%	Ionic	Monomer	370	2100	High	Sodium calcium edatate
Ioxithalamate	Telebrix 30	Ionic	Monomer	300	1710	High	Sodium calcium edatate
Diatrizoate	Hypaque 50	Ionic	Monomer	300	1550	High	Sodium calcium edatate
Ioxaglate	Hexabrix	Ionic	Dimer	320	580	Low	Sodium calcium edatate
Iopromide	Ultravist 370	Non-Ionic	Monomer	370	774	Low	Sodium calcium edatate, Tromethamine
Iohexol	Omnipaque 350	Non-Ionic	Monomer	350	884	Low	Sodium calcium edatate, Tromethamine
Ioversol	Optiray 300	Non-Ionic	Monomer	300	651	Low	Sodium calcium edatate, Tromethamine
Iopamidol	Isovue-370	Non-Ionic	Monomer	370	796	Low	Sodium calcium edatate, Tromethamine
Iobitridol	Xenetix 350	Non-Ionic	Monomer	350	915	Low	Sodium calcium edatate, Tromethamine
Ioxilan	Oxilan 350	Non-Ionic	Monomer	350	695	Low	Sodium calcium edatate, Tromethamine
Iomeprol	Iomeron 350	Non-Ionic	Monomer	350	618	Low	Tromethamine
Iopentol	Imagopaque 300	Non-Ionic	Monomer	300	640	Low	Sodium calcium edatate, Tromethamine
Iodixanol	Visipaque 320	Non-Ionic	Dimer	320	290	Iso	Sodium calcium edatate, Tromethamine
Iotrolan	Isovist 300	Non-Ionic	Dimer	300	291	Iso	Sodium calcium edatate

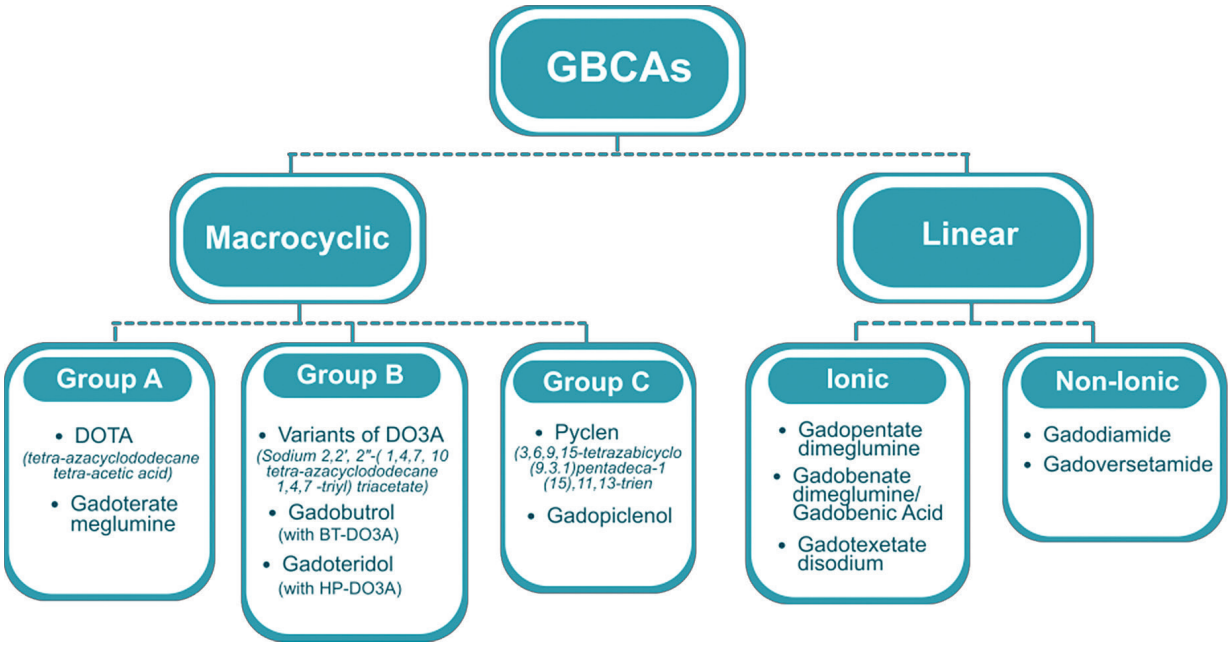


Figure 4. Classification of gadolinium-based contrast agents (GBCAs) according to structural type (macrocyclic vs. linear), with further subdivision based on ionicity (ionic vs. non-ionic) and the chemical structure of the chelating agents (Groups A, B, and C). *Adapted from Vega et al and Gracia Bara et al.*[7,12]

agents.[12] Hypersensitivity reactions (HSRs) to GBCAs have been increasingly reported, paralleling the global rise in MRI utilization involving contrast administration.[13] Although the incidence rates of HSR to GBCA are lower than those associated with ICM, it can range from 0.15% to 0.40%, with severe reactions occurring in approximately 0.002–0.004% of the general population and up to 0.033% among patients undergoing cardiac MRI.[14] These reactions are typically attributed to the gadolinium ion (Gd^{3+}) itself or to the chelating ligand. Gadolinium is a paramagnetic metal ion responsible for the contrast-enhancing effect in MRI; however, in susceptible individuals, it may be recognized by the immune system as a foreign substance, triggering a hypersensitivity response. The chemical design of the chelating agent (such as DTPA or DOTA) may influence both the likelihood and severity of hypersensitivity reactions.[12]

Cross-reactivity among GBCAs is possible, particularly within macrocyclic agents, but is generally rare. Occasional cross-reactivity has been reported between macrocyclic and linear agents, while cross-reactivity among linear GBCAs appears to be uncommon.[7]

Vega and Gracia Bara et al. proposed a classification scheme for GBCAs into three groups based on the chelating agents that may induce hypersensitivity reactions (Figure 4):[7,12]

- Group A: Includes gadoterate meglumine with chelating agent DOTA
- Group B: Includes gadobutrol with chelating agent BT-DO3A and gadoteridol with chelating agent HP-DO3A
- Group C: Includes gadopiclenol with chelating agent pyclen

ADVERSE REACTION TO RADIOCONTRAST MEDIA

Adverse reactions to RCM can range from predictable physiologic reactions to unpredictable hypersensitivity reactions (Figure 5). These reactions are mild in about 5%, moderate in 0.022%, and severe in 0.0025%.[15]

Physiologic reactions

Physiologic reactions, which may be chemotoxic or vasovagal, are related to the chemical properties of RCM and are dependent on the dose and infusion rate. Chemotoxic reactions may range from mild pain at the infusion site, warmth, flushing, and nausea, to severe reactions causing organ toxicity, nephropathy, and thyroid dysfunction. Vasovagal reactions may cause dizziness, hypotension, and bradycardia which are self-limiting and transient. Chemotoxic and vasovagal reactions do not require premedications with subsequent imaging studies, but rather, a different set of management strategies especially for severe chemotoxic reactions (organ toxicity, nephropathy, thyroid dysfunction) which are beyond the scope of this paper.

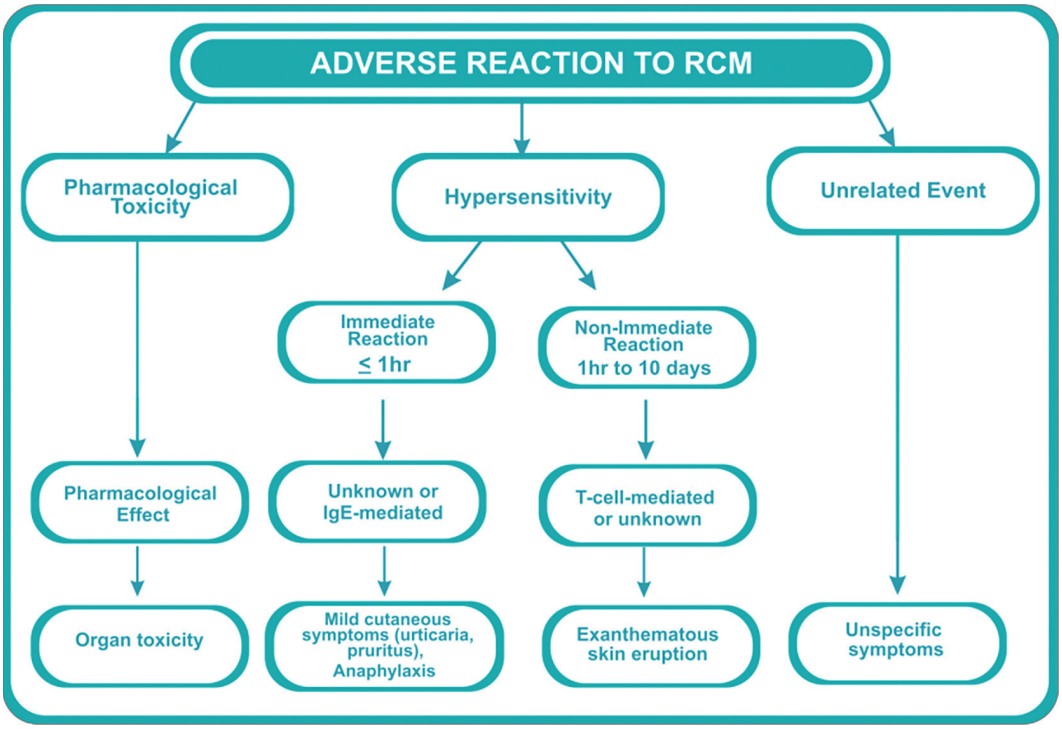
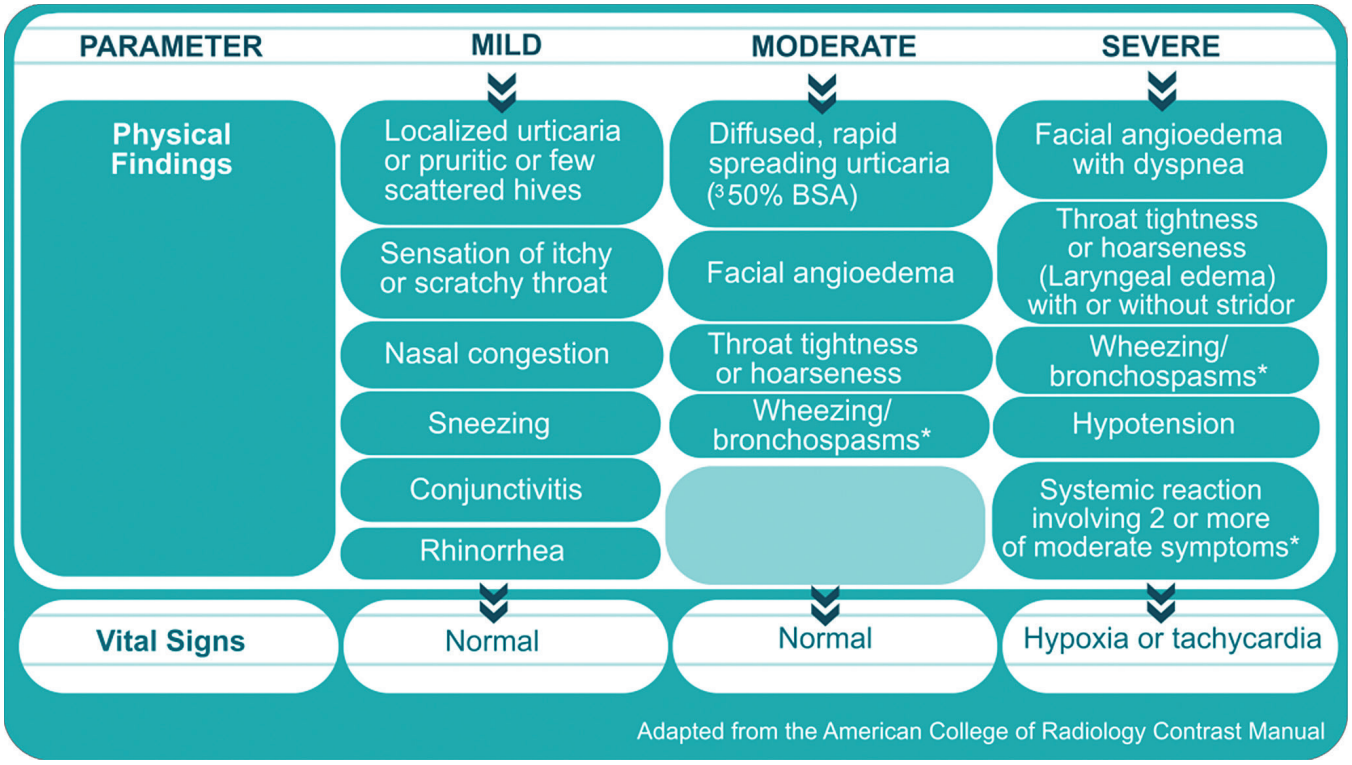


Figure 5. Classification of adverse drug reactions after RCM administration. *Adapted from Brockow et al.*[23]

Table 3. Categories of immediate hypersensitivity reactions to iodinated contrast media. *Adapted from the American College of Radiology*[24]



**Systemic symptoms refer to involvement of additional organ systems.*

Hypersensitivity reactions

Hypersensitivity reactions to RCM (0.5-3%) can be subdivided into immediate hypersensitivity reactions (IHR) and delayed or non-immediate hypersensitivity reactions (NIHR) based on the time interval between RCM administration and the first manifestation of symptoms.[15,16]

Immediate Hypersensitivity Reactions (IHR)

Immediate hypersensitivity reactions occur within one hour after RCM administration. The mechanisms of IHR may be IgE or non-IgE-mediated.[16] Majority of the reactions are non-IgE mediated.[17]

IgE-mediated mechanism, a well-known cause of IHR to RCM,[17] starts with a previous exposure to RCM that may lead to formation of antigen-specific IgE antibodies bound to FcεR1 receptors on the surface of mast cells and basophils. Cross-linking of bound IgE antibodies on cell surface may cause mast cell degranulation and subsequent release of inflammatory mediators.[18]

In non-IgE mediated mechanism, the high osmolality and chemical structure of the contrast agent may cause direct activation of the Mas-related G protein-coupled receptor member X2 (MRGPRX2) receptor in mast cells.[19] This MRGPRX2-mediated mast cell degranulation may trigger the release of preformed mediators such as histamine and tryptase.[20] Furthermore, contrast agents may cause activation of the complement cascade via alternative pathway, leading to the production of anaphylatoxins C3a and C5a.[21] These anaphylatoxins may directly stimulate the release of inflammatory mediators from mast cells and basophils.[21,22] Moreover, bradykinin formation may potentially play a role in the reaction.[17] Accumulation of bradykinin may cause development of angioedema and contribute to symptoms associated with RCM exposure.

Clinical manifestations regardless of the mechanisms are classified based on severity: mild, moderate, and severe, to guide management (Table 3).[23]

Mild

Mild IHRs to RCM present as signs and symptoms that are usually brief (in duration), non- progressive and self-limited, and require no specific treatment.[3,26]

Mild reactions comprise the vast majority of IHR and may manifest as localized urticaria or pruritus or few scattered hives, sensation of itchy or scratchy throat; nasal congestion, sneezing, conjunctivitis, or rhinorrhea associated with normal vital signs (Table 3).[3,24-26]

Most IHRs are driven by the pharmacological characteristics of the contrast medium- specifically its osmolality,

molecular structure, and excipient composition. Lower osmolality and ionic neutrality are associated with reduced activation of biological mediators such as histamine, released from mast cells and basophils.[15] Immediate hypersensitivity reactions to ICM are mediated by the direct or indirect effector cells activation. Minority of these IHRs are considered IgE-mediated with positive skin tests (STs) and elevated serum tryptase levels. ICM may cause non-IgE mediated IHR by stimulating intracellular calcium ion influx in MRGPRX2 receptor and activating mast cell degranulation.[19]

On the other hand, the rate of IHR to gadolinium-based contrast agents (GBCAs) was 0.3% the majority of which were considered as mild presenting as skin rash and hives.[27] Immediate hypersensitivity reactions to GBCAs may be IgE- or non-IgE-mediated *in vitro* studies. The results from the *in vivo* test confirm the role of IgE in the pathogenetic mechanism of IHRs. However, the low positive predictive value of skin tests suggests a non-IgE-mediated activation of mast cells and basophils via the MRGPRX2. Recent study confirms that gadoterate meglumine can directly trigger mast cell activation and degranulation thru this pathway.[28] These non-IgE-mediated mechanisms could explain IHRs during the first exposure.[15]

There are few case reports regarding mild to moderate IHRs to barium sulfate which presented primarily as urticaria and angioedema and were mostly due to excipients in the enema, including methylparaben and carboxymethylcellulose, as barium sulfate is considered inert.[29]

<u>*Moderate*</u>

Moderate IHRs are more pronounced and require medical intervention. They may present with generalized urticaria or erythema, facial edema, throat tightness or hoarseness, and wheezing/bronchospasm without associated marked hypotension or desaturation.[3,24]

First generation ionic ICM with high osmolarity are more frequently associated with IHR compared to the newer non-ionic monomeric (low osmolarity) or dimeric (iso-osmolar) ICM.[3] However, moderate reactions to non-ionic iodinated contrast media have been documented such as shortness of breath and laryngeal edema which resolved within 24 hours after appropriate management.[26]

On the other hand, an observational study noted a few cases of IHRs such as bronchospasm, laryngeal edema, and dyspnea associated with GBCAs. Furthermore, there was no significant difference in the prevalence of IHR between the ionic-macrocylic GBCA (gadoterate meglumine), which offers a stable binding to gadolinium, and the less stable ionic linear GBCA (i.e. gadobenate dimeglumine). This led to the presumption that the occurrence of reactions is not dependent on the chemical structures and stability.[27]

<u>*Severe*</u>

Severe IHRs are often life-threatening and can result in permanent sequelae and/or mortality if not managed promptly.[3] These include facial angioedema with dyspnea, throat tightness or hoarseness (laryngeal edema) with or without stridor, wheezing or bronchospasm, and hypotension with associated hypoxia or tachycardia, often fulfilling the criteria for anaphylaxis.[3,24,26]

In a multicenter study by Laroche et al involving 20 patients with mild to severe reactions to ICM, only histamine and tryptase levels correlated with the severity of the reaction. The results strongly suggested an IgE-related mechanism and a positive correlation between symptom severity and histamine release and mast cell triggering.[30] In other recent studies, elevated MRGPRX2 levels were associated with an increased risk of severe reactions to ICM, which led to the consideration of MRGPRX2 being a biomarker for predicting ICM-induced anaphylaxis.[21]

Conversely, a retrospective study by Granata et al showed that IHR to GBCAs can present with severe respiratory distress, episode of progressive angioedema, arrhythmia with supraventricular tachycardia and proposed that the propensity of GBCAs to bind proteins increases the risk of triggering IHRs.[27]

Several case reports of anaphylaxis associated with barium enema were attributed to the excipients in the enema.[29,31,32]

Non-immediate Hypersensitivity Reactions (NIHR)

Non-immediate or delayed type cell-mediated reactions occur from one hour to several days after exposure to the contrast. The interaction of the drug with specific receptors on activated memory T cells may play an important role, as evidenced by skin biopsies showing perivascular infiltration of CD4 and CD8 T cells.[17] In vitro studies showed that NIHR may require major histocompatibility complex (MHC) involvement in the recognition of and subsequent reaction to contrast media. One proposed mechanism is the pro hapten concept in which contrast media undergo metabolic biotransformation into reactive covalent-binding fragments. These fragments bind to plasma proteins, are internalized by the antigen presenting cells (APC) and are subsequently presented to T cells via MHC II molecule. The pharmacological interaction with immune receptors or p-i concept may provide another explanation. It involves direct binding of the contrast media to the T cell receptor or MHC molecule which may explain the cross-reactivity between structurally related contrast media via immune receptors.

Table 4. Clinical manifestations of non-immediate hypersensitivity reactions. *Adapted from Brockow et al.*[23]

Exanthema (mostly macular or maculopapular drug eruption)
Urticaria, angioedema
Erythema multiforme minor
Fixed drug eruption
Stevens-Johnson syndrome (SJS)
Toxic epidermal necrolysis
Graft-versus-host reaction
Drug reaction with eosinophilia and systemic symptoms (DRESS)
Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE)
Vasculitis

NIHR reactions to iodinated contrast media most commonly manifest as cutaneous reactions. These may range from mild maculopapular exanthema and urticaria to more severe cutaneous adverse reactions, including Stevens–Johnson syndrome/toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms (DRESS). Other reported manifestations include fixed drug eruption, acute generalized exanthematous pustulosis, symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), and vasculitis. The clinical spectrum of delayed hypersensitivity reactions is summarized in Table 4.[23]

RISK FACTORS FOR IMMEDIATE AND NON-IMMEDIATE HYPERSENSITIVITY REACTIONS TO RCM

Recognition of established risk factors is essential to guide safe contrast use, preventive strategies, and appropriate referral for allergy evaluation.

Immediate hypersensitivity reactions

Immediate hypersensitivity reactions range from mild cutaneous symptoms to life-threatening anaphylaxis. Across multiple large observational studies and guideline statements, the strongest and most consistent risk factor for an immediate reaction is a history of a previous hypersensitivity reaction to iodinated contrast media, particularly when the prior reaction was moderate or severe.[4,23] Other risk factors such as personal history of asthma, unrelated drug allergy, and food allergy were previously thought to increase the risk of hypersensitivity reactions to RCM. These findings were based from a dated research on high osmolality CM reactions that were found to have several methodological weaknesses such as the absence of confirmatory evaluation or testing for self-reported atopic conditions.[26,33] Cardiovascular disease and beta-adrenergic blocker use have been associated with increased reaction severity and complexity of management rather than an increased incidence of reactions.[34] Patients with mast cell disorders are recognized as a high-risk group for severe immediate reactions, including anaphylaxis.[17]

Importantly, seafood or shellfish allergy, so-called "iodine allergy," and sensitivity to povidone-iodine have not been shown to independently increase the risk of immediate hypersensitivity reactions to iodinated contrast media and should not be used to restrict contrast use.[35] The mechanism of IHR to ICM is unrelated to its iodine content. Food allergy to crustaceans is an IgE-mediated reaction to the tropomyosin, and not to the iodine content which is not an allergen. These clarifications are consistently emphasized in guidance from the European Society of Urogenital Radiology, the European Academy of Allergy and Clinical Immunology, and the American College of Radiology.

Non-immediate hypersensitivity reactions

Non-immediate hypersensitivity reactions most commonly manifest as maculopapular exanthema, although rare severe cutaneous adverse reactions have been reported. The primary risk factor for NIHR is a history of a prior delayed reaction to iodinated contrast media, with recurrence frequently occurring upon re-exposure to the same or a structurally related agent.[36]

Other contributory factors include repeated or prolonged contrast exposure, prior drug-induced delayed hypersensitivity reactions, and genetic susceptibility.[37] In contrast to immediate reactions, asthma and atopy do not appear to be significant independent risk factors for delayed hypersensitivity responses.

EVALUATION AND RISK STRATIFICATION OF HYPERSENSITIVITY REACTIONS TO RADIOCONTRAST MEDIA

In patients with suspected or confirmed prior hypersensitivity reactions to radiocontrast media (RCM), every effort should be made to identify the specific contrast agent administered- including its brand/trade name and generic name- and to document the date, type and severity of the reaction, the treatment administered and outcome, through a comprehensive clinical history supplemented by all available supporting documentation.

Skin testing (skin prick test or SPT/intradermal test or IDT) and drug provocation test (DPT) or graded challenge should not be performed solely on the basis of isolated risk factors, which include drug allergy, food allergy, stinging insect allergy, family history of hypersensitivity reactions to radiocontrast media (RCM), female sex, asthma, use

of β-blockers or angiotensin-converting enzyme (ACE) inhibitors, or underlying cardiovascular disease. Similarly, diagnostic testing is not indicated in patients with a history of physiologic (non-hypersensitivity) reactions to RCM.

Immediate hypersensitivity reactions

In patients with a history of immediate hypersensitivity reactions (IHR) to iodinated contrast media (ICM) who are scheduled for elective or non-urgent contrast-enhanced imaging, skin testing (ST) by a board-certified allergist may be performed using the available ICM preparations. When feasible, skin testing with the suspected culprit ICM may also be done to help establish causality. It is ideally performed 2–6 months after the reaction when its diagnostic sensitivity is highest.

The reported sensitivity of skin testing for IHR to ICM is highly variable, ranging from 4.2% to 73%, whereas its specificity is high, with reported values of 94.6% for skin prick testing and 91.4%–96.3% for intradermal testing. In a meta-analysis by Yoon et al., the overall negative predictive value (NPV) of skin testing was 93% (95% confidence interval [CI], 86%–96%).[38] In patients with severe IHR in whom the culprit ICM is unknown, skin testing with all available ICM preparations may assist in selecting a potentially safer alternative agent.

However, clinicians should recognize the limitations of skin testing. A negative skin test does not exclude ICM hypersensitivity, as patients with negative skin test results may still develop an immediate reaction upon re-exposure. In addition, the lack of standardized testing methods and protocols limits comparisons across studies and precludes definitive conclusions regarding diagnostic accuracy. Furthermore, skin testing is time-consuming, requires specialized expertise, and demonstrates substantial cross-reactivity among ICM, estimated at 68% (95% CI, 48%–83%).[38]

Following a negative skin test result, a drug provocation test (DPT) or graded challenge with an ICM may be considered to identify a tolerated contrast agent. The reported NPVs of DPT are 97.3% using a cumulative dose of 10 mL and 80% using 50 mL, although these findings are based on limited data.[3] Because DPT carries a risk of inducing hypersensitivity reactions, it should be performed only after appropriate risk stratification, under close medical supervision by a board-certified allergist in a hospital setting. Variability in published DPT protocols, including dosing regimens, should also be considered when interpreting the available evidence.

For Gadolinium-based contrast agents (GBCAs) reactions, skin testing may be considered in a specialist setting, when future GBCA use is likely.[39] Skin testing to GBCAs is ideally done 2-6 months after the reaction and has a negative predictive value of approximately 80–90% in published studies.[15] However, these estimates are imprecise because of limited sample sizes, variable testing protocols, and possible selection bias. A negative skin test reduces, but does not eliminate, the risk of an immediate hypersensitivity reaction.[12,40,41] The positive predictive value is currently uncertain and insufficiently defined; therefore, a positive result should be interpreted in the context of the clinical history and test controls and should not be regarded as definitive proof of clinical allergy in isolation.

Similar to ICM, when future GBCA administration is clinically necessary, DPT is considered the reference method for confirming or excluding clinical hypersensitivity to a specific gadolinium-based contrast agent and for demonstrating tolerance to an alternative agent in selected patients.[15] It should be noted that validated estimates of its sensitivity, specificity, positive predictive value, and negative predictive value are not currently available. The evidence is limited by small sample sizes, retrospective study designs, heterogeneous challenge protocols, variable doses and infusion rates, inconsistent observation periods, and selection bias. There are some published protocols that have used graded or low-dose exposure, sometimes followed by the clinically required dose, with prolonged observation. The protocol should be individualized by the allergist/immunologist in consultation with radiology.[18] If feasible and after individualized risk–benefit assessment, a supervised DPT should be performed by clinicians experienced in drug allergy and in a facility equipped for immediate treatment of anaphylaxis. A negative DPT demonstrates tolerance under the conditions tested but does not guarantee tolerance to every future exposure.[42] A positive DPT strongly supports clinical reactivity to the tested agent and should generally prompt avoidance of that agent. DPT should be performed only in selected patients.[18]

In patients presenting with suspected RCM-induced anaphylaxis, serum tryptase measurement may be done to support the diagnosis of mast cell activation. A serum sample should be obtained as soon as possible, preferably 15 minutes until 4 hours after symptom onset, followed by a baseline sample obtained at least 24 hours after complete resolution of the reaction.[26,43,44] Interpretation should use the patient's baseline and the acute value rather than relying only on a single absolute cutoff. A normal tryptase does not exclude anaphylaxis, especially in reactions presenting predominantly with respiratory or cutaneous symptoms.

Non-immediate hypersensitivity reactions

In patients with non-immediate hypersensitivity reactions presenting as maculopapular exanthem (MPE) following exposure to an unknown ICM, patch testing (PT) and/or intradermal skin testing (IDT) with delayed readings, followed by DPT performed by a board-certified allergist may be considered using the available ICM preparations.[26,37,44] These tests may assist in identifying the culprit agent and selecting a potentially safe alternative ICM. However, clinicians should recognize that current evidence regarding the diagnostic accuracy of allergy testing for NIHR to ICM remains limited.

A meta-analysis reported that if four or more ICM preparations were tested, at least one skin test-negative ICM could be identified in 90% of patients (95% CI, 77%–96%).[36,38] These finding suggests that skin testing in NIHR can facilitate the selection of an alternative contrast agent.

Delayed-reading IDT is ideally performed 1–6 months after complete resolution of the hypersensitivity reaction, when positivity rates are significantly higher (48%) than when testing is performed later (23%; P = 0.02).[45] A recent meta-analysis and large cohort studies reported a negative predictive value (NPV) of 86.1% (95% CI, 72.1%–94.7%) for delayed-reading IDT.[3] Although several studies have demonstrated a specificity approaching 100%, the overall sensitivity remains uncertain.[26] The combined NPV of a negative delayed-reading IDT followed by a negative drug provocation test (DPT) has been reported to range from 90% to 96%. Nevertheless, clinicians should be aware that cross-reactivity among ICM in patients with NIHR remains substantial, with an estimated prevalence of 39% (95% CI, 29%–50%).[38] In patients with fixed drug eruption (FDE) attributed to ICM, patch testing on the site of the previous lesion may be considered, preferably within 1–6 months after resolution of the reaction. However, this technique may not be widely available, may be technically challenging, and may incur additional cost.[3]

In NIHR to GBCA, PT and/or IDT with delayed readings followed by DPT performed by a board-certified allergist may be considered. However, there is no standardized protocol for DPT to GBCA, and chemotoxicity is possible.

In patients with severe cutaneous adverse reactions (SCARs) to RCM, including Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP), *in vivo* diagnostic testing, such as SPT, IDT and DPT, should not be performed because of the potential risk of re-inducing SCARs.[26,44,46]

PREVENTIVE STRATEGIES FOR HYPERSENSITIVITY REACTIONS TO RADIOCONTRAST MEDIA

Preventing recurrent reactions in patients with prior history of RCM hypersensitivity is challenging. This is because of the cross-reactivity between RCM, with higher frequency in ICM with N-(2,3-hydroxypropyl)-carbamoyl side chain and in macrocyclic GBCA. Several international guidelines and studies recommend switching the culprit RCM to a safer alternative contrast agent.[26,44] Choosing an alternative ICM without the carbamoyl side chain reduces the likelihood of a subsequent reaction. However, cross-reactivity between ICM is more complex, and choosing an alternative ICM based on their group classification alone does not always prevent the recurrence of hypersensitivity reaction.

Available evidence on GBCA cross-reactivity remains limited, as it is based on small retrospective studies with heterogenous methodologies. Although selecting a GBCA with a different molecular structure decreases hypersensitivity reactions by 75%, choosing a skin test-negative GBCA appears to be a safer approach.[18]

Therefore, several guidelines recommend selecting an alternative RCM following evaluation by an allergist. Non-contrast imaging or an alternative imaging modality should also be considered if feasible.[18,26]

Immediate hypersensitivity and physiologic reactions

In patients with a history of physiologic (non-allergic) reactions to iodinated contrast media (ICM), such as warmth, flushing, nausea, or vasovagal reactions, subsequent administration of any available ICM may proceed without premedication. Likewise, premedication is not recommended when the only identified risk factors are drug allergy, food allergy, stinging insect allergy, family history of RCM hypersensitivity, female sex, asthma, use of β-blockers or angiotensin-converting enzyme (ACE) inhibitors, or a history of cardiovascular disease.[26,47]

For patients with a history of mild or moderate IHR to an unknown ICM who require urgent imaging, subsequent contrast-enhanced imaging should be performed using an agent from Group B or Group D. This recommendation is based on the higher likelihood that the culprit ICM belongs to Group A. Likewise, ICM belonging to Group C should be avoided whenever possible, because of their high probability of cross-reactivity with group A (Tables 1 and 5). If the culprit GBCA is unknown, choose an alternative GBCA (Figure 4 and Table 5). However, if the culprit RCM is known, switching to an alternative RCM

Table 5. Guide on selecting an alternative radiocontrast media. *Adapted from Van Der Molen et al.*[44]

Iodine-based contrast media (ICM)	
Involved ICM	**Suggestion regarding the selection of alternative ICM based on clinical practice reports**
When the involved ICM is known	
ICM is from Group A	Alternative ICM from Group B or D (without classic carbamoyl sidechain) *High cross-reactivity between Group A-Group C*
ICM is from Group B	Alternative ICM from Group A, C or D
ICM is from Group C	Alternative ICM from group B (without classic or methyl-modified carbamoyl sidechain)
ICM is from Group D	Alternative ICM from Group A or B (without methyl-modified carbamoyl sidechain)
When the involved ICM is unknown	
Due to the higher likelihood that the involved ICM is from group A	Choose the alternative ICM from Group B or D *High cross-reactivity between Group C-Group A*

Gadolinium-based contrast agents (GBCA)	
Involved GBCA	**Suggestion regarding the selection of alternative GBCA based on practical experience**
When the involved GBCA is known	
GBCA is from Group A	Alternative GBCA from Group B
GBCA is from Group B	Alternative GBCA from Group A
GBCA is from Group C	*Insufficient data for empiric change advice*
When the involved GBCA is unknown	
It is not possible to recommend a regimen with certainty.	
Due to the probability of involvement, using a GBCA different from the one routinely administered is suggested.	
Group A ICM: iohexol, iodixanol, iomeprol, ioversol **Group B ICM:** iopamidol **Group C ICM:** iopromide **Group D ICM:** iobitridol **Group A GBCA:** gadoterate meglumine **Group B GBCA:** gadoteridol, gadobutrol **Group C GBCA:** gadopiclenol ***GBCA*** gadolinium-based contrast agent, *ICM* iodine-based contrast medium	

**AI-assisted table*

belonging to a different group based on cross-reactivity is recommended[26,44] (Table 5).

For non-urgent imaging of patients with prior history of moderate IHR to RCM, a referral to a board-certified allergist for diagnostic testing is recommended when feasible. A skin test (SPT/ IDT)-negative and DPT-negative RCM should be selected for the imaging procedure.[44]

In patients with mild IHR, premedication is not necessary. Evidence supports the strategy of using an alternative ICM rather than relying on premedication alone. A systematic review and meta-analysis involving 7,155 patients with prior IHR to ICM demonstrated that switching to an alternative ICM reduced the risk of breakthrough reactions by 61%.[8] Furthermore, studies by Abe et al. and McDonald et al., found that the use of an alternative ICM provided greater protection against recurrent immediate hypersensitivity reactions than premedication with systemic glucocorticoids.[48]

In a 10-year single-center cohort of 702,917 contrast-enhanced CT scans, ICM–induced anaphylaxis was rare (20.3 per 100,000 scans). Of these reactions, 3% were biphasic, 10% were refractory and 13% were life-threatening.[49] Most episodes occurred in patients who had not received premedication. However, among patients with a history of prior contrast reactions, approximately two-thirds developed recurrent anaphylaxis despite premedication with systemic glucocorticoids and/or antihistamines. Such breakthrough reactions suggest that substituting the culprit ICM with an alternative agent may be more effective in reducing recurrence of anaphylaxis than premedication alone. It appears that premedication

provides only partial protection and should not replace individualized risk assessment, selection of an alternative contrast agent when appropriate, and preparedness for prompt recognition and immediate treatment with epinephrine.[48,49]

In addition, potential adverse effects of premedication, including hyperglycemia from systemic glucocorticoids and sedation or drowsiness from antihistamines, should be carefully considered, particularly in patients with relevant comorbidities.[3,26]

For patients with moderate IHR to RCM, premedication may be considered particularly in those at high risk because of multiple comorbidities or when the consequences of a recurrent reaction would be significant; however, the supporting evidence for its effectiveness remains of low quality. Therefore, the decision to administer premedication should be individualized through shared decision-making, balancing the potential benefits against the risks and allowing patients to participate in informed treatment decisions.[26,44]

In patients with a history of severe IHR or anaphylaxis to a contrast agent, non-contrast imaging or an alternative imaging modality should be considered first whenever diagnostically appropriate.[26] If an alternative imaging is not feasible and contrast-enhanced imaging is urgently required, administration of an alternative ICM from Group B or Group D, or an alternative GBCA is recommended (Table 5) with premedication. For non-urgent procedures, a referral to a board-certified allergist for diagnostic testing is recommended when feasible. A skin test (SPT/ IDT)-negative and DPT-negative RCM should be selected to be given with premedication. Clinicians should recognize that breakthrough reactions may still occur despite premedication (approximately 2.1%), and nearly one-half of these reactions may be moderate to severe.[26,44]

If no alternative RCM is available, a multidisciplinary discussion is recommended before deciding to proceed with the RCM administration. The selection of the specific alternative RCM should be made in consultation with the allergy and radiology specialists. The procedure should be performed in a setting where advanced resuscitation facilities are readily available.[50]

Non-immediate hypersensitivity reactions

In patients with non-immediate hypersensitivity reactions (NIHR) presenting as maculopapular exanthem to an unknown RCM who require urgent imaging, switching to an alternative ICM from Group B or Group D, or an alternative GBCA is recommended (Table 5). For non-urgent imaging, a referral to a board-certified allergist for diagnostic testing is recommended when feasible. A diagnostic test (PT/IDT with delayed reading/DPT)-negative RCM should be selected for the imaging procedure.[44]

When the culprit RCM is known, switching to an alternative RCM belonging to a different group based on cross-reactivity is recommended (Table 5).

Current evidence does not support the routine use of premedication to prevent recurrent NIHR presenting as MPE.[26]

In patients with severe cutaneous adverse reactions (SCARs) to RCM, such as Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP), non-contrast imaging or an alternative imaging modality should be first considered if feasible. If a contrast-enhanced imaging is indispensable, strict avoidance of all ICM is recommended if the culprit is an ICM. Likewise, strict avoidance of all GBCA is recommended if the culprit is a GBCA.[26,44]

Patient labeling and medical record documentation

Patients with prior hypersensitivity reactions to RCM should not be broadly labeled as having a generic "radiocontrast media allergy," "dye allergy," “iodine allergy” or "gadolinium allergy". A detailed medical documentation must include the specific contrast agent (brand/trade name and generic name), the date, type and severity of the reaction, as well as the treatment administered and outcome. Agents that were tolerated during supervised DPT after a negative skin test or subsequent uneventful contrast-enhanced procedures should be documented specifically as agent-specific tolerance, rather than as blanket tolerance to all contrast agents or blanket avoidance of future contrast agents.

Management of hypersensitivity reactions to RCM

The acute management of hypersensitivity reactions to RCM is beyond the scope of this position statement.

Limitations of the evidence

These consensus recommendations are based on the best available evidence to date. However, the overall quality and certainty of the evidence remain limited because of several important factors: (a) the low incidence of moderate to severe hypersensitivity reactions associated with modern low-osmolar, nonionic iodinated contrast media, which limits the feasibility of large, adequately powered studies; (b) the scarcity of methodologically rigorous investigations; and (c) substantial heterogeneity among published studies, including differences in premedication regimens, skin testing protocols, patient selection criteria, contrast media evaluated, and strategies for selecting alternative contrast agents.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Data Availability Statement

No datasets were generated or analyzed for this study.

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