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DIAGNOSTIC STRATEGIES FOR CONTRAST MEDIA HYPERSENSITIVITY IN RADIOLOGY PRACTICE

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ABSTRACT

Iodinated contrast media (ICM) and gadolinium-based contrast agents (GBCA) support most contrast-enhanced imaging, and modern agents carry a low risk of adverse reactions. Hypersensitivity reactions (HSRs) still occur and range from mild urticaria to fatal anaphylaxis. Clinicians classify HSRs as immediate (IHRs, onset within 1 hour) or non-immediate (NIHRs, later onset, most often after 1 to 3 days). IHRs arise through IgE-mediated or non-IgE mechanisms, while NIHRs reflect T-cell-mediated hypersensitivity and present as maculopapular exanthem or, in rare cases, severe cutaneous adverse reactions. Unverified “iodine allergy” labels and reliance on premedication expose patients to suboptimal imaging and breakthrough reactions. This narrative review synthesizes 12 publications from 2021 to 2025 on the diagnosis of ICM and GBCA hypersensitivity. Skin prick and intradermal tests (IDT) form the core of the work-up, and pooled positivity reaches 52% after severe IHRs. A pooled analysis of 1,137 patients found that IDT up to undiluted ICM raised sensitivity from 0.282 to 0.774 with no loss of specificity. Patch tests and delayed-reading IDT identified the culprit in 47.6% to 85% of patients in recent NIHR cohorts. Basophil activation tests add diagnostic yield after severe IHRs, while lymphocyte-based assays remain research tools. Drug provocation tests confirm tolerance of a skin-test-negative alternative, and a negative test predicts tolerance in more than 90% of re-exposures. Switching to a skin-test-negative agent outperforms premedication with the culprit agent. We propose a four-step diagnostic pathway for adults and children.

Keywords: Contrast media; Gadolinium; Drug hypersensitivity; Skin tests; Basophil activation test; Drug provocation test

1 INTRODUCTION

Contrast media help clinicians distinguish tissues and improve diagnostic accuracy in computed tomography (CT), angiography, and magnetic resonance imaging (MRI).¹ Radiology departments administer more than 70 million doses of ICM worldwide each year,² and some estimates place the figure at several hundred million.³ Most patients tolerate

these agents. A minority develop adverse drug reactions (ADRs), and ADRs occur more often with X-ray contrast media than with agents used for ultrasound or MRI.¹

ADRs fall into two groups. Chemotoxic, or type A, reactions depend on dose and concentration and include warmth, flushing, nausea, vasovagal episodes, and nephrotoxicity.^{1,2,4} Type A reactions account for more than 80% of all ADRs to contrast media.⁴ Hypersensitivity, or type B, reactions (HSRs) appear independent of dose and form the subject of this review.^{1,4} An imprecise label such as “iodine allergy” can steer clinicians away from the most informative examination, and premedication with the culprit agent fails to prevent all recurrences.^{1,2}

Earlier work considered most immediate reactions non-allergic, or “anaphylactoid”.^{2,5} Positive skin tests, tryptase release, and positive basophil activation tests now support an IgE-mediated mechanism in a subset of patients, most of them with severe reactions.^{2,6} Non-immediate reactions resemble T-cell-mediated drug allergy in timing, morphology, and test results.^{1,2} These findings give allergy testing two roles: to confirm or exclude allergy to the culprit agent, and to identify a safe alternative for future imaging.^{2,4} This review summarizes the evidence on diagnostic tools for ICM and GBCA hypersensitivity, examines the debate over intradermal test concentration, and proposes a diagnostic pathway for radiology practice.

2 METHODS

We conducted a narrative review of 12 publications from 2021 to 2025 that address the diagnosis and management of contrast media hypersensitivity. The set comprises three narrative reviews,^{1,2,4} one pooled analysis of published intradermal test data,³ four clinical cohorts of ICM hypersensitivity,^{7–10} one case series of life-threatening ICM anaphylaxis,⁶ and three studies of GBCA hypersensitivity.^{5,11,12} We extracted data on clinical classification, mechanisms, test methods and concentrations, diagnostic performance, cross-reactivity, drug provocation protocols, and prevention, and we synthesized the findings by topic.

3 CONTRAST AGENTS, ADVERSE REACTIONS, AND CLINICAL PHENOTYPES

3.1 Contrast Agents

Water-soluble ICM share a tri-iodinated benzene ring. Ionic monomers reach five to seven times the osmolality of serum, non-ionic monomers two to three times, and non-ionic dimers such as iodixanol are iso-osmolar.¹ Ionic monomers caused frequent adverse events, and radiology practice has replaced them with non-ionic agents.^{3,9} The excipients sodium calcium edetate and tromethamine can also cause hypersensitivity, so a complete work-up considers them.¹ GBCA fall into linear and macrocyclic classes according to the structure of the gadolinium-binding chelate.^{5,12}

3.2 Epidemiology and Risk Factors

With standardized definitions, the incidence of hypersensitivity to non-ionic ICM ranges from 0.37% to 0.99%, and the combined incidence of IHRs and NIHRs from 0.5% to 3%.¹ A Korean cohort of 196,081 patients showed an overall prevalence of 0.73% and severe reactions in 0.01%.² Anaphylactic shock follows 0.04% to 0.28% of administrations, and fatal anaphylaxis about 1 to 2 per 100,000 procedures.^{1,2} NIHRs make up an estimated 0.5% to 23% of all HSRs to contrast material.^{7,8} For GBCA, HSRs follow about 0.07% of injections, with severe reactions in 0.52 per 10,000 injections.¹² Delayed reactions to GBCA appear rare.⁵

A previous reaction to ICM is the strongest risk factor. In the Korean cohort, re-exposure after a previous reaction carried an adjusted odds ratio (OR) of 199. Hyperthyroidism (OR 3.6), drug allergy (OR 3.5), other allergic disease (OR 6.8), and a family history of contrast reactions (OR 14.0) acted as minor risk factors.² Other reported factors include asthma, cardiac disease, anxiety, age, female sex, injection dose and speed, and the absence of contrast warming.^{1,4}

3.3 Immediate and Non-Immediate Reactions

IHRs begin within 1 hour of administration and most often within 30 minutes. About 70% begin within 5 minutes, and life-threatening reactions occur within 20 minutes in all but a few cases.^{1,6} Brockow notes that some IHRs begin up to 6 hours after injection.² Most IHRs present with urticaria, angioedema, and pruritus. Anaphylaxis adds respiratory involvement (bronchospasm, wheezing, laryngeal edema), gastrointestinal involvement (nausea, vomiting, abdominal pain, diarrhea), or cardiovascular involvement (tachycardia, hypotension), and an acute coronary syndrome from reduced coronary blood flow can develop.^{1,2}

NIHRs begin more than 1 hour after injection, most often after 1 to 3 days and up to 10 days later.^{2,4} Some authors set the threshold at 6 hours.^{2,7} Maculopapular exanthem (MPE) is the most common form and accounts for more than half of NIHRs.¹ Delayed urticaria-like rash, fixed drug eruption, and symmetrical drug-related intertriginous and flexural

exanthema also occur.^{1,9} 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), remain rare.^{1,2} Table 1 compares the two phenotypes.

Table 1: Clinical classification of contrast media hypersensitivity reactions

Feature	Immediate HSR (IHR)	Non-immediate HSR (NIHR)
Onset	Within 1 hour, most within 30 minutes; about 70% within 5 minutes ^{1,6}	After 1 hour (some authors use 6 hours); most after 1–3 days, up to 10 days ^{2,4,7}
Mechanism	IgE-mediated allergy, or non-IgE activation (MRGPRX2, complement, contact system) ^{1,2,12}	T-cell-mediated (type IV) hypersensitivity ^{1,2}
Main clinical features	Urticaria, angioedema, pruritus; anaphylaxis with respiratory, gastrointestinal, or cardiovascular involvement ^{1,2}	Maculopapular exanthem, delayed urticaria-like rash, fixed drug eruption; rare SCARs (SJS/TEN, DRESS, AGEP) ^{1,2,9}
Main diagnostic tests	SPT, IDT with 15–20 min reading, acute tryptase, BAT ^{1,2,6}	Patch test, delayed-reading IDT, LTT ^{1,2,9}
Role of premedication	Suppresses most mild non-allergic reactions; less reliable in severe allergic reactions; breakthrough reactions occur ^{1,2}	Not effective ^{1,4,9}

AGEP, acute generalized exanthematous pustulosis; BAT, basophil activation test; DRESS, drug reaction with eosinophilia and systemic symptoms; HSR, hypersensitivity reaction; IDT, intradermal test; LTT, lymphocyte transformation test; SCAR, severe cutaneous adverse reaction; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis; SPT, skin prick test.

3.4 Pathophysiological Mechanisms

Two pathways lead to IHRs. In IgE-mediated allergy, drug-specific IgE bound to the high-affinity receptor FcεRI on mast cells and basophils cross-links on re-exposure, and the cells release histamine, tryptase, and other mediators.^{1,11} Non-IgE pathways include direct mast cell activation through the receptor MRGPRX2, complement activation, activation of the factor XII contact system with bradykinin generation, and formation of pseudoantigens.^{1,2,4,12} A non-IgE mechanism could explain why some patients react on first exposure.⁴

The share of IgE-mediated reactions depends on the population studied. Most patients with mild IHRs show no sensitization, while positive skin tests cluster in severe and recent reactions.^{2,4} In a series of eight patients with life-threatening ICM anaphylaxis, seven (87.5%) had a positive skin test or basophil activation test, and five of the eight reactions occurred on first exposure.⁶ For GBCA, no study has yet demonstrated gadolinium-specific IgE.¹¹

NIHRs reflect T-cell-mediated (type IV) hypersensitivity.^{1,2} Skin biopsies show CD4⁺ and CD8⁺ T-cell infiltrates, and delayed-reading skin tests, positive lymphocyte transformation tests, and ICM-specific T-cell clones support this mechanism.^{1,2,9} In an Italian cohort, 10 of 19 patients with positive skin tests (52.6%) reacted at their first ICM exposure. The authors proposed earlier sensitization to unknown chemical structures, as described for muscle relaxants.⁹

4 INDICATIONS AND TIMING OF THE ALLERGY WORK-UP

4.1 Patient Selection and Documentation

Testing serves patients with a credible HSR history, such as urticaria, angioedema, bronchospasm, anaphylaxis, MPE, fixed drug eruption, or AGEP. Patients with subjective or non-specific symptoms, such as warmth, nausea, injection-site erythema, headache, or dizziness, have a low pretest probability and gain nothing from testing. The same applies to patients labeled “iodine allergic” and to patients with food, venom, or drug allergies but no previous contrast reaction.² Experts advise against prescreening unselected patients with skin tests, because a prospective study found low sensitivity and a low positive predictive value for prescreening IDT.^{1–3}

Accurate records underpin this selection. The record should state the name, dose, and concentration of the culprit agent, the manifestations and their chronology, and the treatment given, and staff should avoid the term “iodine allergy”.¹ In a French cohort, 58.1% of patients had no record of the agent involved.¹⁰

4.2 Timing

Test sensitivity falls as the interval from the reaction lengthens.^{1,2} One review recommends a work-up between 1 and 6 months after the reaction,¹ and other authors recommend 6 weeks to 6 months.^{4,9} In a European multicenter study cited

by Caron et al., 50% of patients tested within 6 months had positive tests, compared with 22% of patients tested later.¹⁰ Gamboa et al. found a shorter interval in skin-test-positive NIHR patients (median 2 months) than in skin-test-negative patients (median 5 months).⁸ Caron et al. found the opposite pattern, with a mean interval of 111 months.¹⁰

5 SKIN TESTING

The test panel includes the culprit and, where possible, a range of alternative agents. If the culprit is unknown, the allergist tests the broadest available panel.^{2,4} The suspected mechanism determines the test method (Table 2).²

Table 2: Diagnostic modalities for contrast media hypersensitivity

Modality	Principle	Main clinical role	Advantages	Limitations	Reported performance
Skin prick test (SPT)	Mast cell degranulation in the skin ^{1,2}	First step for IHR ^{1,2}	High specificity ^{1,2}	Low positivity (3% in IHR, 7% in NIHR) ^{1,4}	Specificity 94.6%–95% ^{1,2}
Intradermal test (IDT)	Intradermal injection read at 15–20 min (IHR) or 24–72 h (NIHR) ^{2,4}	Core test for IHR and NIHR; identifies alternatives ^{2,4}	Higher yield than SPT; concentration can be stepped up ^{1,3}	Optimal concentration unsettled ^{2,3}	Sensitivity 0.282 (diluted) vs. 0.774 (undiluted); specificity 0.983 vs. 1.000 ³
Patch test	Delayed T-cell response to undiluted agent ^{2,9}	NIHR ^{2,9}	Simple, safe ⁹	Readings over several days; lower sensitivity than IDT in some series ^{1,2}	Positive in 43.2% of one NIHR cohort ⁹
Basophil activation test (BAT)	Flow cytometry of CD63/CD203c after ex vivo stimulation ^{6,11}	Severe IHR; adjunct to skin tests ^{1,6}	No risk to patient ^{6,11}	Cut-offs not validated; false positives with amidotrizoate ^{2,6}	ICM: sensitivity 46%–63%, specificity 88%–100% ^{1,2} ; GBCA: sensitivity 80%, specificity 85%–100% ¹¹
Lymphocyte transformation test (LTT)	Proliferation of drug-specific memory T cells ^{1,4}	Research tool for NIHR ⁴	Detects T-cell sensitization ^{1,4}	Variable sensitivity; affected by corticosteroids ^{1,4}	Sensitivity 13%–75% ^{1,4}
Drug provocation test (DPT)	Controlled intravenous administration ^{2,4}	Reference standard; confirms tolerance of alternative ^{2,4}	Confirms tolerance before imaging ²	Risk of severe reaction; no standard protocol ^{1,2,4}	NPV >90% in real-life re-exposure ²

GBCA, gadolinium-based contrast agent; ICM, iodinated contrast media; IHR, immediate hypersensitivity reaction; NIHR, non-immediate hypersensitivity reaction; NPV, negative predictive value.

5.1 Immediate Reactions

For IHRs, the allergist starts with a skin prick test (SPT) using undiluted ICM at 300 to 320 mg iodine/mL and proceeds to IDT if the SPT is negative.^{1,2} IDT dilutions range from 1:1000 to 1:10.¹ Schmid et al. advise starting at 1:1000 or 1:100 after a severe reaction and at 1:10 after a mild one.³ The allergist injects 0.02 to 0.05 mL to raise an initial wheal of 3 to 5 mm and reads the test at 15 to 20 minutes.^{3,7,12} A wheal increase of 3 mm or more with surrounding erythema, compared with the saline control, counts as positive.^{9,12} Lower test concentrations give lower positivity rates.¹ GBCA testing follows the same principle, with undiluted SPT and IDT at 1:10.^{5,11,12}

5.2 Non-Immediate Reactions

For NIHRs, the work-up combines patch tests with undiluted ICM and IDT with delayed readings.^{2,4} Readings take place at 24 to 48 and 72 hours, and patients should return for further readings, up to 7 days for IDT, if a test site reacts.^{2,4} Chiu

and Chu describe a stepwise sequence that begins with a patch test and progresses to delayed IDT at 1:10 and then to undiluted ICM.¹ A positive delayed IDT shows erythematous induration at the injection site.^{7–9} In fixed drug eruption, tests applied to a previous lesion site avoid false-negative results, because drug-specific resident memory T cells persist there.^{1,4}

Table 3: Skin testing approaches and results in recent studies

Study population	Tests and concentrations	Reading times	Main findings	Reference
Pooled data, 1,137 patients (IHR and NIHR)	IDT diluted ($\leq 1:10$) vs. up to undiluted	Immediate and delayed	Culprit positive 31.0% vs. 72.5%; sensitivity 0.282 vs. 0.774; no irritant reactions in 154 controls	³
74 patients with IHR to ICM	SPT undiluted; IDT 1:100,000 to 1:10	20 min	8.1% positive; recurrence in 12.5% of re-exposed skin-test-negative patients (NPV 88.1%)	¹⁰
37 patients with NIHR to ICM	Patch test undiluted; IDT 1:1000 to 1:10 if patch test negative	Patch: D2, D4, D7; IDT: 20 min, D1–D3	51.4% positive (16 patch, 3 IDT); all 16 iobitridol-negative patients tolerated iobitridol	⁹
42 patients with NIHR, most to iomeprol	SPT and IDT undiluted	24, 48, 72 h	47.6% positive; 53% of challenges with skin-test-negative agents tolerated	⁸
20 patients with MPE, DRESS, or AGEP to ICM	Delayed IDT 1:10 and undiluted	6–48 h	Culprit identified in 85%; iohexol–iodixanol cross-reactivity 100%	⁷
9 patients with IHR to GBCA	SPT undiluted; IDT 1:10	20 min	NPV 100% on two-step challenge	¹²

AGEP, acute generalized exanthematous pustulosis; D, day; DRESS, drug reaction with eosinophilia and systemic symptoms; GBCA, gadolinium-based contrast agent; ICM, iodinated contrast media; IDT, intradermal test; IHR, immediate hypersensitivity reaction; MPE, maculopapular exanthem; NIHR, non-immediate hypersensitivity reaction; NPV, negative predictive value; SPT, skin prick test.

Table 3 summarizes recent cohorts. Bianchi et al. tested 37 patients with NIHRs, using patch tests first and IDT from 1:1000 to 1:10 when patch tests were negative. Skin tests identified the culprit in 19 patients (51.4%), 16 by patch test and 3 by IDT.⁹ Gamboa et al. performed SPT and IDT with undiluted ICM in 42 patients with NIHRs, most of them to iomeprol. Tests were positive in 20 patients (47.6%), all on delayed reading, and all 22 patients with negative tests reacted on challenge with the culprit.⁸ Copaescu et al. performed delayed IDT at 1:10 and undiluted in 20 patients with MPE, DRESS, or AGEP. Delayed IDT identified the culprit in 17 patients (85%), and 3 patients needed a challenge to confirm the diagnosis.⁷ Brockow considers IDT more sensitive than patch testing in NIHRs.² Bianchi et al., in contrast, found most positive results on patch testing and raised positivity from 43.2% to 51.4% by adding IDT.⁹

5.3 Diagnostic Performance

Skin test performance depends on reaction severity and test timing.^{1,2} In a meta-analysis cited by Chiu and Chu, pooled per-patient positivity reached 17% in IHRs and 52% after severe IHRs. In NIHRs, it reached 26%, with rates of 7% for SPT, 22% for IDT, and 16% for patch tests.¹ SPT specificity reaches 94.6% to 95%, and IDT specificity at 1:10 reaches 91.4% to 96.3% in IHRs.^{1,2} In NIHRs, reported sensitivity and specificity reach 72% and 96%, and the specificity of delayed tests approaches 100%.^{1,2}

The negative predictive value (NPV) matters most for selecting an alternative agent. For alternative ICM, Chiu and Chu report an NPV of 94.2% after IHRs and 86.1% after NIHRs.¹ Caron et al. followed 40 re-exposed patients and observed recurrent IHRs in 5 (12.5%) despite negative skin tests, an NPV of 88.1%. One patient with a negative work-up to iodixanol received it again by accident and developed a grade IV reaction, more severe than the first.¹⁰ In NIHRs, Gamboa et al. found that patients tolerated 35 of 66 challenges (53%) with skin-test-negative agents.⁸ After an alternative skin-test-negative ICM, IHRs recur in 7% and NIHRs in 35% of patients.¹ A negative skin test therefore lowers the risk of recurrence without removing it, and the residual risk is greatest in NIHRs.^{1,8}

5.4 Diluted (1:10) Versus Undiluted Intradermal Testing

The maximum test concentration for IDT remains unsettled. Most centers dilute ICM 1:10 for IDT to improve specificity,² and Brockow states that undiluted IDT raises sensitivity at the cost of specificity.² Caron et al. consider undiluted IDT a source of irritant reactions and call for further study.¹⁰ Other groups test with undiluted ICM, and several authors recommend undiluted IDT for non-immediate reactions alone.^{1,3,4}

Schmid et al. addressed this question in a pooled analysis of individual data from 1,137 patients in 29 original studies. Of these patients, 797 had diluted IDT and 340 had IDT up to undiluted ICM. The authors applied meta-analysis criteria to study selection but did not perform a formal meta-analysis.³ Undiluted testing produced more positive tests (24.7% vs. 9.0%; $P < 0.0001$; OR 0.30) and more positive culprit agents (72.5% vs. 31.0%; $P < 0.0001$; OR 0.17). Sensitivity reached 0.774 with undiluted testing and 0.282 with diluted testing, and specificity reached 1.000 and 0.983. Patients in the diluted group underwent drug provocation testing (DPT) more often (46.9% vs. 26.2%; OR 2.54). Among patients challenged after IDT, the NPV reached 1.000 after undiluted testing and 0.925 after diluted testing.³

Schmid et al. found no reports of irritant or non-specific reactions in the 13 studies that used undiluted IDT. None of 154 controls tested with undiluted ICM reacted, whereas 5 of 295 controls (1.7%) tested with diluted ICM did.³ Copaescu et al. confirmed non-irritant results for undiluted delayed IDT in 10 healthy controls.⁷ Schmid et al. found that most papers using diluted ICM gave no supporting citation for that choice. Their analysis also showed more undiluted testing in NIHR patients, which may explain the higher positivity reported for NIHRs.³ The authors propose SPT with undiluted ICM, followed by IDT that starts at 1:1000 or 1:100 after severe reactions and at 1:10 after mild reactions, with progression to undiluted ICM when the 1:10 step is negative.³ The pooled design limits these conclusions, because the source papers seldom reported patients with negative tests and few included controls.³

6 IN VITRO AND EX VIVO TESTS

6.1 Serum Tryptase

Serum tryptase drawn within 1 to 4 hours of an IHR supports the diagnosis of anaphylaxis, and a second sample 24 hours later serves as the baseline.^{1,2} Of the published definitions of a relevant rise, $(1.2 \times \text{baseline tryptase}) + 2 \mu\text{g/L}$ has the highest Youden index.¹ Tryptase levels correlate with IHR severity,¹ and a significant change occurred in six of eight patients with life-threatening anaphylaxis.⁶ After mild reactions, tryptase seldom rises, which limits its role in that setting.⁴

6.2 Basophil Activation Test

The basophil activation test (BAT) uses flow cytometry to measure activation markers such as CD63 or CD203c on basophils after ex vivo stimulation with the contrast agent.^{6,11} It detects both IgE-mediated and non-IgE-mediated activation, and it carries no risk for the patient beyond venipuncture.^{6,11} In ICM IHRs, reported sensitivity ranges from 46% to 63% and specificity from 88% to 100%, depending on the threshold.^{1,2,4} The choice of stimulant, protocol, gating strategy, and cut-off all influence performance, and no large study has validated BAT.^{1,2}

Li et al. tested eight patients with life-threatening ICM anaphylaxis. BAT was positive to the culprit in five patients (62.5%), two of whom had negative skin tests, and the combination of both tests raised detection to 87.5%.⁶ Standard cut-offs (5% CD63 and 10% CD203c upregulation, with a stimulation index [SI] above 2.0) gave false-positive results to amidotrizoate in 29% of tests, and higher cut-offs reduced them. Skin tests and BAT disagreed across the agents tested, and neither test alone detected all sensitized patients.⁶

For GBCA, Cabrera et al. derived cut-offs from receiver operating characteristic (ROC) curves in 40 healthy controls and five women with IHRs to gadoteric acid or gadobutrol. At a 1:100 dilution of gadoteric acid, a CD63 threshold of 4.6% gave a sensitivity of 80% and a specificity of 85%, and an SI threshold of 2.79 gave a sensitivity of 80% and a specificity of 100%. BAT detected one patient with negative skin tests. The study included five patients, which limits the precision of these estimates.¹¹

6.3 Lymphocyte Transformation Test and Other Assays

The lymphocyte transformation test (LTT) measures proliferation of drug-specific memory T cells after stimulation with the culprit agent.^{1,4} Its sensitivity ranges from 13% to 75%, and a negative result does not exclude the culprit.^{1,4} Saretta et al. classify LTT as a research tool.⁴ Copaescu et al. performed an interferon-gamma (IFN- γ) ELISpot assay in four patients with NIHRs confirmed by delayed IDT. The assay failed to identify the culprit in all four patients. The authors also found the ICM concentrations cytotoxic to patient cells.⁷

7 DRUG PROVOCATION TESTING

DPT serves as the reference standard for diagnosing contrast HSRs. It carries a risk of severe reactions and requires trained staff and resuscitation equipment.^{4,6} Clinicians use it in three situations: to exclude allergy when skin tests to the culprit are negative, to confirm tolerance of a skin-test-negative alternative before the next contrast examination, and to clarify an uncertain history.^{1,2,4} Some centers proceed to re-exposure in the radiology department without a prior DPT, because this approach appears safe. The choice depends on reaction severity, DPT availability, and local experience.^{2,4} Contraindications include renal insufficiency or nephrotoxic medication, hyperthyroidism or thyrotoxic crisis, radioactive iodine therapy, pregnancy and breastfeeding, lactic acidosis, and a history of SJS, TEN, or DRESS.^{1,2} Chiu and Chu also list severe IHRs, whereas Brockow favors DPT with a skin-test-negative alternative after severe anaphylaxis.^{1,2}

No standard protocol exists.^{1,2,10} Reported ICM protocols range from graded schedules, such as up to four steps starting at one-tenth of the dose at 1-hour intervals, to single doses of 15 mL, 0.5 mL/kg, or 100 mL.^{1,4,6–8} Dose affects the result. One Spanish center reported an NPV of 97.3% with 10 mL and 80% with 50 mL.¹ Copaescu et al. noted that their 15 mL challenge fell below the 50 to 80 mL used for CT and may have produced false-negative results.⁷

For GBCA, Stehlin et al. gave an intravenous placebo of 5 mL saline, followed by 1 mL and 4 mL of a skin-test-negative agent at 30-minute intervals. All nine patients tolerated the alternative without an IgE-type reaction, and the 4 mL step revealed dose-dependent non-IgE reactions in two patients.¹² A negative DPT with a skin-test-negative agent predicts tolerance in more than 90% of real-life re-exposures.²

8 CROSS-REACTIVITY AND SELECTION OF ALTERNATIVE AGENTS

8.1 Iodinated Contrast Media

Avoiding the culprit and selecting a skin-test-negative alternative form the basis of secondary prevention.^{1,2} Cross-reactivity complicates this choice. Sources disagree on which phenotype shows more of it. Brockow and Gamboa et al. report more cross-reactivity in NIHRs, whereas pooled skin test data cited by Chiu and Chu show 68% in IHRs and 39% in NIHRs.^{1,2,8} Positive tests to several ICM appeared in 67% of 97 patients, independent of chemical class.⁴

Statistical analyses have grouped ICM by shared side chains. Group A (iodixanol, iohexol, iomeprol, iopamidol, ioversol, ioxithalamate) shares N-(2,3-dihydroxypropyl)carbamoyl side chains, group B contains iobitridol, which carries an N-methyl side chain, together with ioxaglate, and group C contains amidotrizoate.^{6,8,9} Gamboa et al. found 22% cross-reactivity between iomeprol and iopamidol in NIHRs and placed both agents in the same group.⁸ Copaescu et al. found complete cross-reactivity between iohexol and its dimer iodixanol: all 15 patients with a positive delayed IDT to iohexol also tested positive to iodixanol.⁷

Iobitridol has attracted interest as an alternative in NIHRs, and Brockow links its low cross-reactivity to a different side chain.² Bianchi et al. found positive tests to iobitridol in 3 of 19 sensitized patients (15.8%), and all 16 patients with negative tests tolerated iobitridol. No patient sensitized to iodixanol reacted to iobitridol, but 3 of 8 patients sensitized to iomeprol (37.5%) did.⁹ Other cohorts urge caution. Three of five iomeprol-allergic patients challenged with iobitridol did not tolerate it,⁸ and iobitridol cross-reacted on delayed IDT in 3 of 5 iohexol-allergic patients.⁷ These data support selecting the alternative by testing, because individual predisposition outweighs chemical similarity.^{4,8}

8.2 Gadolinium-Based Contrast Agents

GBCA hypersensitivity is rare, and most reactions are immediate.⁵ Grueber et al. reviewed 28 patients with skin-test-proven GBCA allergy. Macrocyclic agents, led by gadobutrol and gadoterate, triggered most reactions, and all delayed MPE followed gadobutrol. Cross-reactivity appeared in about 29% of patients, within macrocyclic agents or between macrocyclic and linear agents, and never among linear agents. Patients tolerated re-exposure to skin-test-negative agents.⁵ Stehlin et al. observed similar patterns: monosensitization to one macrocyclic agent, cross-sensitization among macrocyclic agents, and no cross-reactivity between a linear culprit and gadobutrol. Skin tests showed an NPV of 100% in their nine challenged patients, compared with 86% to 89% in earlier studies.¹²

9 PREMEDICATION AND OTHER PREVENTIVE MEASURES

Premedication with an H1-antihistamine and a corticosteroid remains the most common preventive regimen. A standard protocol combines diphenhydramine 50 mg 1 hour before contrast with prednisone 50 mg at 13, 7, and 1 hour before contrast.^{1,2} Premedication suppresses most mild to moderate non-allergic reactions.² Its benefit in true allergy

remains unproven. It is less reliable in severe allergic reactions, does not prevent NIHRs, and gives a false sense of security.^{1,2,4}

Clinical data confirm these limits. Breakthrough reactions in premedicated patients occur at three to four times the rate seen in patients without a previous reaction.¹ In the Italian NIHR cohort, eight patients (21.6%) reacted despite premedication.⁹ After mild reactions, adding a corticosteroid to an antihistamine gave no further benefit.² Corticosteroids raise blood pressure and blood glucose, disturb diabetic control, and cause leukocytosis, infection, prolonged hospitalization, and drowsiness.^{1,2}

After mild reactions, recurrence reached 31.1% with the same ICM, 12% with a different ICM, and 7.6% with antihistamine premedication.¹ Both Brockow and Chiu and Chu conclude that changing from the culprit to a different ICM outperforms premedication.^{1,2} In patients with a positive skin test to the culprit, the clinician can give a skin-test-negative alternative without premedication, under emergency preparedness.² Premedication keeps a place as an added precaution after severe IHRs, in patients who cannot undergo skin tests, and in non-allergic reactions with negative tests.^{2,4}

General measures also lower the risk. Slower injection, a lower dose, and warming of the contrast medium show an association with lower IHR rates.² Rapid drug desensitization has been described for urgent use, but sources disagree on the evidence for contrast media.^{1,2,4}

10 PEDIATRIC CONSIDERATIONS

HSRs to contrast media appear rarer in children than in adults, and pediatric guidelines are lacking.⁴ In more than 100,000 administrations, children aged 1 to 9 years had a severe reaction rate of 0.07%. Among more than 11,000 doses of non-ionic low-osmolality ICM in children and neonates, 20 patients (0.18%) had acute allergic-like reactions, 80% of them mild, compared with 0.6% in adults from the same population. Reported pediatric risk factors include female sex, a previous contrast reaction, asthma, and previous allergic-like reactions to other agents.⁴ Two pediatric SCARs have been reported.⁴

Saretta et al. adapt the adult work-up to children and note that its results lack pediatric validation. They recommend SPT with undiluted ICM, IDT at 1:10 (undiluted in NIHRs), and patch tests with undiluted ICM in NIHRs, with IDT readings at 20 minutes and, for delayed reactions, at 48 and 72 hours.⁴ The pediatric premedication protocol uses oral or intravenous methylprednisolone 0.5 mg/kg at 13, 7, and 1 hours, with chlorphenamine 1 mg (1 to 5 years), 2 mg (6 to 12 years), or 4 mg (over 12 years) 1 hour before ICM. After anaphylaxis, the authors favor unenhanced CT or MRI, and children with SCARs should not receive contrast media.⁴

11 PROPOSED DIAGNOSTIC PATHWAY

We propose a four-step pathway based on these data (Figure 1; Table 4).²⁻⁴

- **Step 1, clinical characterization.** The clinician confirms the culprit agent, dose, and route from radiology records, separates HSRs from chemotoxic and unrelated reactions, classifies the HSR as immediate or non-immediate, and grades severity.^{1,2} Patients with non-specific symptoms need no testing.²
- **Step 2, allergy work-up.** Six weeks to 6 months after the reaction,^{4,9} the allergist performs SPT and IDT for IHRs, and patch tests with delayed-reading IDT for NIHRs. Testing progresses from diluted to undiluted concentrations when earlier steps are negative.^{1,3} Acute tryptase and BAT support the diagnosis after severe IHRs.^{1,6}
- **Step 3, alternative agent screening.** The allergist tests a panel of alternative ICM or GBCA and selects a skin-test-negative agent.^{2,4,5}
- **Step 4, controlled re-exposure.** The team confirms tolerance by DPT or by re-exposure in the radiology department under emergency preparedness, with DPT favored after severe anaphylaxis.² After SJS, TEN, or DRESS, clinicians avoid ICM and use MRI with GBCA or non-contrast imaging.^{2,4} The team documents the culprit agent, test results, and recommendations in a standardized format.^{1,3}

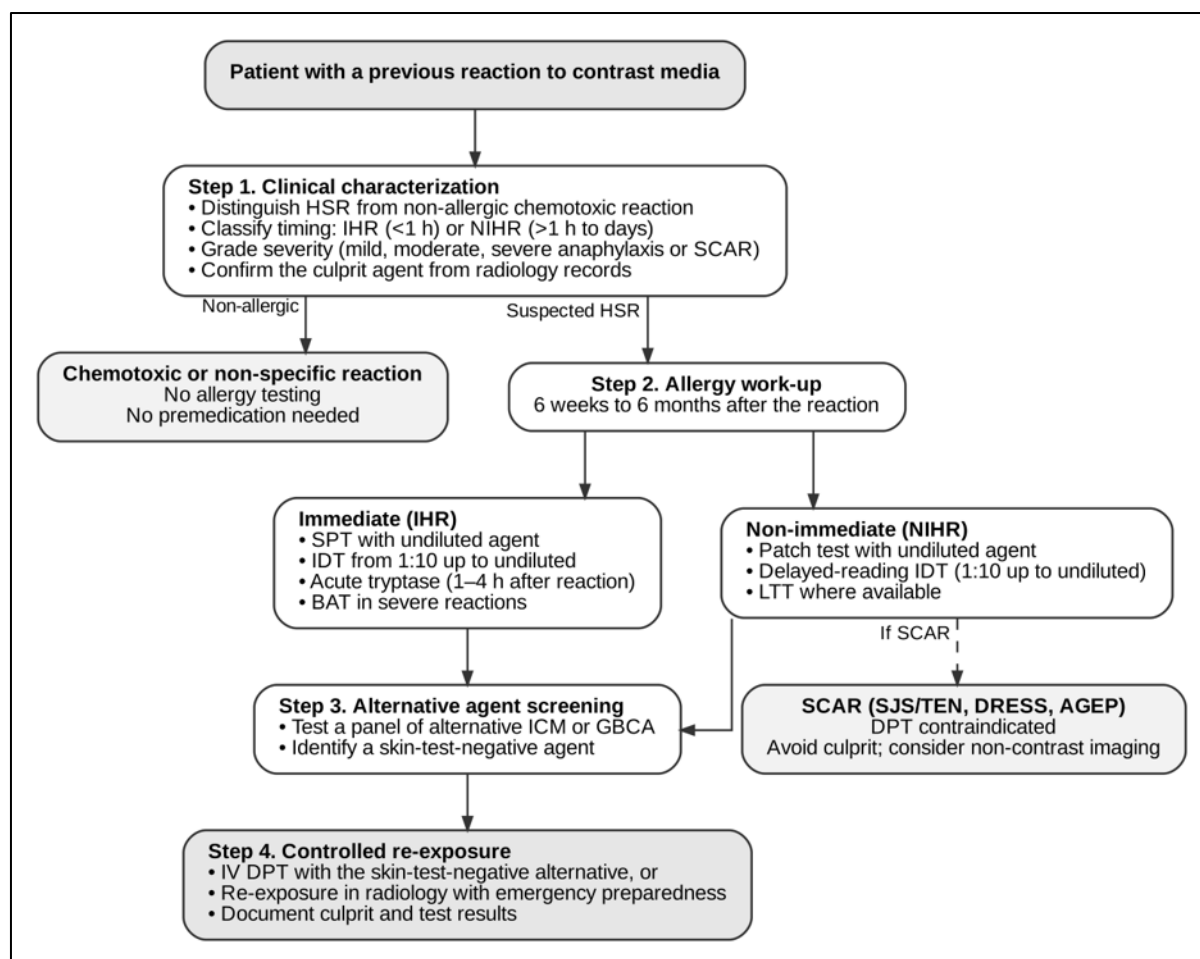


Figure 1: Proposed diagnostic pathway for patients with a previous hypersensitivity reaction to contrast media, adapted from published algorithms. 2–4 Step 1 separates hypersensitivity from chemotoxic reactions and grades severity. Step 2 tailors the allergy work-up to reaction timing, 6 weeks to 6 months after the event. Step 3 screens alternative agents, and Step 4 confirms tolerance by controlled re-exposure. The dashed arrow marks the branch for severe cutaneous adverse reactions, in which drug provocation testing is contraindicated. AGEP, acute generalized exanthematous pustulosis; BAT, basophil activation test; DPT, drug provocation test; DRESS, drug reaction with eosinophilia and systemic symptoms; GBCA, gadolinium-based contrast agent; HSR, hypersensitivity reaction; ICM, iodinated contrast media; IDT, intradermal test; IHR, immediate hypersensitivity reaction; IV, intravenous; LTT, lymphocyte transformation test; NIHR, non-immediate hypersensitivity reaction; SCAR, severe cutaneous adverse reaction; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis; SPT, skin prick test

Table 4: Proposed diagnostic approach by patient category

Patient category	Initial diagnostic step	Secondary step	Clinical management	References
Non-specific or chemotoxic symptoms	Clinical history	No testing	No allergy work-up	1,2
Mild IHR (urticaria, angioedema)	SPT and IDT with culprit and panel	DPT with culprit if tests negative, or alternative agent	Skin-test-negative alternative under emergency preparedness	2,4
Severe IHR (anaphylaxis)	Acute tryptase; SPT and IDT, stepped up to undiluted	BAT; DPT with skin-test-negative alternative	Skin-test-negative alternative; avoid culprit and skin-test-positive agents	2,3,6

Benign NIHR (MPE)	Patch test and delayed-reading IDT	LTT where available; DPT	Skin-test-negative alternative confirmed by challenge	2,7–9
SCAR (SJS/TEN, DRESS)	Skin tests with caution	DPT contraindicated	Avoid ICM; MRI with GBCA or non-contrast imaging	2,4

BAT, basophil activation test; DPT, drug provocation test; DRESS, drug reaction with eosinophilia and systemic symptoms; GBCA, gadolinium-based contrast agent; ICM, iodinated contrast media; IDT, intradermal test; IHR, immediate hypersensitivity reaction; LTT, lymphocyte transformation test; MPE, maculopapular exanthem; NIHR, non-immediate hypersensitivity reaction; SCAR, severe cutaneous adverse reaction; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis; SPT, skin prick test.

12 EVIDENCE GAPS AND FUTURE RESEARCH

Most cohorts are small, come from one or two centers, and select patients with well-phenotyped reactions.^{6–8,12} The optimal IDT concentration needs prospective comparison within the same patients, and the effect on test results of the 350 to 400 mg/mL agents used in radiology remains unknown.³ BAT and LTT need cut-offs validated against healthy control populations, and larger cohorts.^{2,11} DPT protocols differ in dose, steps, and intervals, and few studies have challenged skin-test-positive patients to establish the positive predictive value.^{7,10,12} Cross-reactivity patterns, including the place of iobitridol after iomeprol allergy, require larger series.^{8,9} Pediatric diagnostic protocols remain unvalidated.⁴

Abbreviations

- **ADR**, adverse drug reaction;
- **AGEP**, acute generalized exanthematous pustulosis;
- **BAT**, basophil activation test;
- **CT**, computed tomography;
- **DPT**, drug provocation test;
- **DRESS**, drug reaction with eosinophilia and systemic symptoms;
- **GBCA**, gadolinium-based contrast agent;
- **HSR**, hypersensitivity reaction;
- **ICM**, iodinated contrast media;
- **IDT**, intradermal test;
- **IFN- γ** , interferon-gamma;
- **IHR**, immediate hypersensitivity reaction;
- **LTT**, lymphocyte transformation test;
- **MPE**, maculopapular exanthem;
- **MRI**, magnetic resonance imaging;
- **NIHR**, non-immediate hypersensitivity reaction;
- **NPV**, negative predictive value;
- **OR**, odds ratio;
- **ROC**, receiver operating characteristic;
- **SCAR**, severe cutaneous adverse reaction;
- **SI**, stimulation index;
- **SJS**, Stevens-Johnson syndrome;
- **SPT**, skin prick test;
- **TEN**, toxic epidermal necrolysis.

13 CONCLUSIONS

ICM and GBCA hypersensitivity includes IgE-mediated, non-IgE-mediated, and T-cell-mediated reactions, and precise phenotyping guides the work-up. Skin tests form the core of diagnosis. Their yield rises with reaction severity, a short interval from the reaction, and higher test concentrations, and IDT up to undiluted ICM shows greater sensitivity without loss of specificity. BAT adds diagnostic yield after severe IHRs, while LTT and ELISpot remain research tools. A skin-test-negative alternative, confirmed by DPT or controlled re-exposure, protects patients better than premedication with the culprit agent. A structured pathway shared by radiologists and allergists allows safe contrast-enhanced imaging for most patients with a previous reaction.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

The author declares no conflicts of interest.

Author Contributions

- M.Q.B.Z.: conceptualization, literature review, writing (original draft), writing (review and editing).
- K.H.H. : writing (review and editing), validation

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