Immediate and nonimmediate hypersensitivity reactions to iodinated contrast media (ICM) have been reported to occur in a frequency of about 0.5%-3% of patients receiving nonionic ICM. The diagnosis and management of these patients vary among guidelines published by various national and international scientific societies, with recommendations ranging from avoidance or premedication to drug provocation test. This position paper aims to give recommendations for the management of patients with ICM hypersensitivity reactions and analyze controversies in this area. Skin tests are recommended as the initial step for diagnosing patients with immediate and nonimmediate hypersensitivity reactions; besides, they may also help guide on tolerability of alternatives. Re-exposition or drug provocation test should only be
done with skin test-negative ICMs. The decision for performing either re-exposition or drug provocation test needs to be taken based on a risk-benefit analysis. The role of in vitro tests for diagnosis and pretreatment for preventing reactions remains controversial.

**KEYWORDS**

Iodinated contrast media, hypersensitivity, allergy, IgE, T cells, diagnosis, management

## 1 | INTRODUCTION

Adverse events after iodinated contrast media (ICM) administration may be either hypersensitivity reactions (type B reactions) or toxic reactions (type A reactions). According to the time interval between ICM administration and appearance of symptoms, hypersensitivity reactions are divided into immediate reactions (IHR), which occur within 1 (to 6) hours after ICM administration, or non-immediate reactions (NIHR), appearing more than 1 hours after ICM exposure. Both IHR and NIHR have been reported to occur in a frequency of about 0.5%-3% of patients receiving nonionic ICM.

IHR induce anaphylaxis, urticaria, angioedema, sometimes together with vomiting, abdominal pain, diarrhea, or more severe reactions affecting the respiratory and cardiovascular systems with dyspnoea, bronchospasm, and/or a sudden drop in blood pressure. Hypotension may be associated with loss of consciousness (anaphylactic shock). In about 70% of these reactions, the onset is within 5 minutes after injections.

NIHR commonly manifest as maculopapular exanthema (MPE) and rarely as more severe reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), fixed drug eruption (FDE), drug reaction with eosinophilia and systemic symptoms (DRESS), symmetric drug-related intertriginous and flexural exanthema (SDRIFE), or acute generalized exanthematous pustulosis (AGEP). In addition, delayed-appearing urticaria or angioedema may occur, especially within the first 6 hours after ICM administration.

The management of patients with previous hypersensitivity reactions to ICM varies among guidelines published by various national and international scientific societies, with recommendations ranging from avoidance or premedication to drug provocation test (DPT). Table 1. This position paper aims to give recommendations for the management of patients with ICM hypersensitivity reactions and analyze controversies in this area. It updates previous recommendations by the EAACI IG Drug Allergy/European Network on Drug Allergy (IGDA/ENDA) taking into account new data and developments.

## 2 | METHODS

This position paper was commissioned by the European Academy of Allergy and Clinical Immunology (EAACI). It is based on evidences and on expert opinion. The preparation included a literature search in MEDLINE by the members of the Task Force Group focusing on the search of the words (radio and iodinated) contrast, adverse reactions, hypersensitivity, and allergy. We restricted the content of this paper to hypersensitivity reactions. During the development of these guidelines, the consultation process included meetings in Amsterdam in April 2018, in Munich in May 2018, in November 2018 in Zurich, a telephone conference in November 2018, and in June 2019 in Lisbon. Comments, suggestions, and recommendations were carefully considered and consented by the whole group. For each statement, the quality of evidence and recommendation was graded and discussed, confirmed, or amended by consensus of the Task Force members. Grading for key statements was performed adopting the GRADE system.

Evidence was graded as high, low, or very low based on expert opinion considering available evidence, because no systematic review was done. The strength of the recommendations was strong or weak, that is, the grading of low/strong in the text denotes a low quality of evidence or great strength of recommendation.

## 3 | IMMEDIATE HYPERSENSITIVITY REACTIONS

The mechanism underlying IHRs to ICM is still a matter of controversy and, although in the majority of patients the mechanism is nonallergic, in some cases IgE-mediated allergic reactions are reported. The presence of positive skin tests (ST) and basophil activation tests (BAT) and older studies reporting detection of low levels of specific IgE to ICM indicate an IgE-mediated mechanism. Histamine and tryptase serum levels, as well as the frequency of positive allergy diagnostic tests, increase with the severity of the reaction. A recent multicenter prospective study documented allergy in one in tenth, a quarter, half and all patients with cutaneous, moderate-systemic, life-threatening anaphylaxis, and cardiac arrest, respectively. The risk for IgE-mediated allergy increases when three or four different organs are affected simultaneously, especially when cardiovascular symptoms appear in combination with respiratory or cutaneous reactions.
IHRs in the context of a contrast-enhanced image-guided procedure are in most cases (74%) contrast media-induced reactions. In the remaining 26%, other culprit substances/cases such as latex, adenosine, or vasovagal reaction could be identified.

3.1 | What are indications for testing?

3.1.1 | Background

The most significant risk factor for an IHR to a ICM is a previous immediate reaction. Other presumed risk factors (gender, asthma, atopy, allergy to other drugs) have shown inconsistent results and therefore cannot be used as prerequisite for performing ICM allergy work-up.

3.1.2 | Practical statement

Allergy testing is indicated in patients with history of IHR. There are no indications for testing patients labeled as "iodine allergy" (povidone iodine, crustaceans, and mollusk) as well as patients with food, respiratory, cutaneous, and drug allergies, but no previous reaction to ICM. Besides, it is not indicated in patients with unspecific symptoms (generalized pruritus, heat sensation, transient erythema, flushing, dizziness, nausea, sneezing, rhinorrhea, chest tightness) or localized cutaneous reaction (isolated wheals, erythema) at the ICM injection site.

### TABLE 1 Management of patients with previous hypersensitivity reaction to ICM

<table>
<thead>
<tr>
<th>Management</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoidance</td>
<td>Safety</td>
<td>Diagnosis not achieved</td>
<td>To be considered in patients in which other diagnostic options (eg, magnet resonance tomography) are applicable</td>
<td>3,5</td>
</tr>
<tr>
<td>Premedication</td>
<td>Easy</td>
<td>Breakthrough reactions in patients with severe previous reactions</td>
<td>Weak evidence of its effectiveness</td>
<td>52-62,98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>False sense of security</td>
<td>Probably not helpful for preventing severe allergic HR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No evidence for benefit</td>
<td>Often done in the USA but considered controversial in Europe</td>
<td></td>
</tr>
<tr>
<td>Alternative by Clinical History</td>
<td>Easy</td>
<td>Reduction of reaction rates</td>
<td>Use of different ICM more effective compared with premedication</td>
<td>66,67</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weak evidence</td>
<td>Difficult to identify the culprit ICM in clinical records</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Time-consuming</td>
<td>Increasing evidence that DPT is safe</td>
<td>10,26,51,69,77,89</td>
</tr>
<tr>
<td>Alternative by ST-negativity</td>
<td>High negative predictive value</td>
<td>Exclusion of ICM highly suspected not to be tolerated</td>
<td>Increasing evidence</td>
<td>21,29,32,37,46,47,51,69,76,77,83,92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Only few patients with IHR will have positive ST</td>
<td>Recommended in Europe by allergists</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>More useful in NIHR</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>No prediction for nonsevere nonallergic reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alternative by DPT-negativity</td>
<td>Approach when ICM administration is needed</td>
<td>ICM dose can be titrated</td>
<td>Increasing evidence that DPT is safe</td>
<td>10,26,51,69,77,89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time-consuming</td>
<td>Previously avoided because of severe reactions when radiologists used pretest dosages</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Hospitalization necessary</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Expertise needed also for emergency treatment</td>
<td></td>
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<td></td>
<td></td>
<td>Risk stratification needed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.2 | How to perform skin testing?

3.2.1 | Background

IHRs to ICM have traditionally been perceived as nonallergic reactions; therefore, ST has been considered as an inappropriate tool.
for the diagnosis of such reactions, although this view has changed by newer evidence.25 The sensitivity of STs in IHR varies from 4.2% to 73% among different studies.5,13,20-30 A meta-analysis revealed positive rates of 17% (95% CI, 10%-26%), being up to 52% (95% CI, 31%-72%) for severe reactions.29 In a large study, positive STs were observed in 26% of patients reporting IHR; 3% had positive skin prick test (SPT) and 25% positive intradermal test (IDT).6 The specificity of SPT is estimated at 94.6% and of IDT 91.4%-96.3%.6,20 Negative predictive value (NPV) of ST with ICM has been reported to be 93% (95% confidence interval, 86%-96%) in a meta-analysis.29 A French study reported high NPV of ST for ICM (94.2% (95% CI 89.6% to 97.2%) for IHR).21 Only one Spanish study reported that only 62.5% of their patients were diagnosed by ST and 37.5% by DPT.26 In the same center, NPV was 97.3% or 80% when DPT was done by injecting 10 mL or 50 mL, respectively.31

Such variability may be due to patient selection, the clinical symptoms of the patients, their severity, the ICM substance used, the time interval between the reaction and the study, and that DPT cannot differentiate allergic from nonallergic IHR as it is the case with other drugs.32-34 If this time is within 2-6 months, 50% of patients tested show positive results, decreasing to up 18% for patients tested at other time points (earlier than 2 months or later than 6 months).6 The reason for this fact may be the limited duration of skin reactivity due to IgE clearance.35

3.2.2 | Practical statement

ST and IDT should be performed according to EAACI Guidelines.36 ICM should be used undiluted at the iodine concentration of 300-320 mg/mL for SPT and diluted 1:10 for IDT.5,6 STs should be performed with the ICM involved in the reaction, if known.5,10 as it has been reported that 56.7%37 to 86% of patients with positive STs gave positive results to the culprit.3 It has been reported that a total of 18.2% were positive to two ICM and 27.3% to three or more.6 Therefore, STs should be performed with the broadest possible panel of ICM available in the department if the result is positive or if the culprit is unknown.5,10

Recommendations

- **When to test:** STs are preferably performed within 2-6 months after the reaction (weak/low).
- **What to test:** STs should be performed with the ICM involved in the reaction if known (strong/high). If the result is positive or if the culprit ICM is unknown, STs should be performed with the broadest possible panel of ICM (strong/moderate).
- **How to test:** ICM should be used undiluted at 300-320 mg/mL for SPT and diluted at 1:10 for IDT (strong/moderate). STs should start by performing SPT and, if negative, continue with IDT (strong/moderate).

### 3.3 | What is the value of in vitro testing?

There are different in vitro methods used in IHR to ICM: histamine, tryptase, and cysteinyl leukotrienes (cysLT) determination at the acute phase of the reaction and BAT for identifying the ICM involved in the reaction once the reaction has resolved.

3.3.1 | Histamine, tryptase, and cysteinyl leukotrienes

**Background**

Histamine is released from mast cells and basophils after IgE-mediated reactions and concentrations measured in plasma few minutes after reactions correlate with severity. Histamine can also be released from basophils in vivo through non-IgE-mediated pathways.14,15,38 Tryptase is continually secreted by mast cells in tissues, and then, it diffuses into the circulation, where it can be measured as protryptase. This can undergo additional processing within the cell to become mature tryptase, which is secreted only during mast cell activation. De novo synthesized cysLT may also mediate ICM-induced IHR.39

**Practical statement**

Histamine and tryptase can be both measured to confirm IHR to ICM. However, histamine is degraded quickly, being less specific and more complicated to measure by commercially available assays. Thus, tryptase is regarded as the preferred mediator. The approach is to compare acute (within 4 hours of the event) and baseline total tryptase levels (at least 24 hours after all signs and symptoms of the event have subsided) to distinguish between an increased mast cell burden (eg, mastocytosis, in which baseline tryptase levels remain elevated) and mast cell degranulation (with only acute tryptase levels elevated). The minimal elevation of acute over baseline tryptase levels suggested to be clinically significant is calculated as at least 2 ng/mL+ [1.2 x baseline tryptase level]10 or at least 20% above baseline plus 2 ng/mL during or within 4 hours after a symptomatic period.41 An increase from baseline level during allergic symptoms is suggestive of an IHR to ICM. It has been reported that higher tryptase elevations are indicative of IgE-mediated mast cell activation and correlate with the clinical severity of the reaction.15,20,42

**Recommendation**

- Tryptase determination at the acute phase is useful for confirming IHR to ICM, if a transient increase is detectable (strong/moderate).
3.3.2  |  Basophil activation tests

**Background**

BAT is a flow cytometry-based cellular assay that measures activation of basophils upon allergen stimulation. It has shown utility for diagnosing IHR to drugs.28,43 Regarding ICM, three studies demonstrate a BAT sensitivity of 46%-63% depending on the threshold chosen and a specificity of 89%-100%.13,26,44 The area under the ROC curve was 0.79 (95% confidence interval 0.67-0.91, P < .0001) by using the stimulation index as the diagnostic criteria with 1:100 dilution of RCM.24

**Practical Statement**

BAT can be a complementary tool to diagnose IHR to ICM,5 showing good correlation with ST and DPT results.26 It may be especially useful in cases with severe reaction and contraindications for ST or DPT.5 It is important to take into account that certain factors may affect BAT result, such as the time between the reaction and the test or the severity and type of reaction.26 However, the NPV has not been clearly determined.45 In addition, it has to be considered that about 10% of patients have nonreacting basophils (positive-control negative), rendering this test unsuitable for these patients.

**Recommendation**

- BAT can be an additional tool for diagnosing patients with IHR with severe reactions or those with high risk (weak/low).

3.4  |  Is there a role for Drug Provocation Test?

3.4.1  |  Background

DPT is the final step of the diagnostic algorithm because of potential risk to the patient, and it is used when there is no other available diagnostic tool. Moreover, it can be used to find a safe alternative. However, controversy still exists about the need of DPT with ICM, with most studies coming from Europe.10,21,26,31,32,37,46,47 In the American Guidelines, there is no statement favouring DPT with ICM in IHRs.48 Studies from Japan indicated severe reactions to very small “pretest doses”,49 which has hampered development of DPT for many years. Even in patients without reaction to “pretesting,” severe reactions have been reported following ICM re-exposure.50 However, these older studies used pretesting not after ST as a tool for risk stratification prior to re-exposure; therefore, potential IgE-mediated allergic patients were left unidentified. New studies seem to indicate that DPT could be a safe procedure, presenting the same risks as with other drugs when higher doses are used, and it is performed in experienced centers.10,13,26,32

Besides hypersensitivity reactions, ICM can induce contrast-induced acute kidney injury, which may lead to end-stage renal disease and even death, thyrotoxic crisis, and lactic acidosis. Therefore, only trained allergists who adhere to necessary safety recommendations should perform DPTs with ICM.

3.4.2  |  Practical statement

Either re-exposition in a needed radiological examination or DPT can be done either to confirm tolerance with the ST-negative culprit ICM or with an ST-negative alternative ICM in patients with positive ST to the culprit ICM or in patients with an anaphylactic reaction in which administering the culprit is contraindicated.5,9

A broad safety check is necessary in every patient who will undergo DPT with ICM, especially in patients with kidney risk factors. It is recommended to determine the serum creatinine, to calculate the estimated glomerular filtration rate (eGFR) and to monitor these parameters after DPT. DPT is contraindicated in patients with risk factor for kidney injury and renal insufficiency, in patients who receive nephrotoxic medication, in patients with contrast-enhanced image-guided examination less than one week ago, or in whom a diagnostic contrast administration is planned in the next 1-7 days. DPT is also contraindicated in patients who will undergo a radioiodine therapy as well as in patients with hyperthyroidism. Pregnant and breastfeeding women should be excluded from DPT. Metformin medication should be stopped 24 hours before the DPT and can be reintroduced if the follow-up does not reveal a renal function alteration. As prophylaxis against renal damage, it is recommended to give

**Recommendations**

- Either re-exposition or DPT can be performed to confirm tolerance to a skin test-negative ICM; the decision is based on availability of DPT and risk-benefit analysis (strong/high).
- DPT with ICM can be done as a diagnostic test either with the culprit or with an alternative ICM (strong/high).
- Available protocols should be standardized and validated (strong/high).
- Renal function needs to be carefully monitored (strong/high).
- As in any DPT, the decision needs to be taken based on a risk-benefit analysis of each patient and should be done only in well-equipped centers and by trained personnel in immediate emergency treatment (strong/low). The possibility to perform the DPT together with the radiological examination should be considered (strong/low).
- DPT is not indicated in patients at risk (renal complaints, hyperthyroidism, radioactive iodine therapy, pregnant and breastfeeding women, nephrotoxic medication, etc) (strong/high).
low-osmolality or isosmolar ICM and check renal function before injection.27

As with other drugs, there is no consensus regarding the dose of ICM during DPT, with doses ranging from 49 to 100 mL. The protocols are as follows: (i) 5-15-30-50 mL (cumulative dose = 100 mL) at 45-min intervals 26; (ii) 0.05-0.5-1-5-7.5-10-25 mL (cumulative dose = 49.05 mL) at 30-minutes intervals.51

3.5 | When is premedication recommended?

3.5.1 | Background

Premedication with systemic corticosteroids and H1 antihistamines has been widely used to reduce the rate of IHR although its effectiveness has not been properly documented, and there is no gold standard of premedication regimens. Moreover, premedication is not able to suppress all IHRs and some patients may develop breakthrough reactions.

Usually, the premedication protocol consists in a combination of a multidose corticosteroid and an antihistamine (eg, prednisone 13 hours, 7 hours, and 1 hours prior to ICM exposure with diphenhydramine 1 hours prior to ICM exposure).56-58 Lee et al54 reported the result of a study to evaluate the benefit of a severity-tailored prophylaxis in patients at risk of recurrent hypersensitivity reactions to ICM. Chlorpheniramine and methylprednisolone were recommended according to a severity index, and an alternative ICM based on a negative ST was used for patients with near-fatal anaphylactic shock or life-threatening reactions. In the group of patients with mild reactions, the prophylaxis with antihistamines plus corticosteroids did not produce significant beneficial outcomes compared with pretreatment with only antihistamines. However, in patients with severe reactions, the frequency of breakthrough reactions was reported to decrease when patients were premedicated with chlorpheniramine and corticosteroids two and 12 hours before. In general, using an alternative ICM protected for developing a reaction. They recommended that for patients with mild reactions, antihistamines can be a safe alternative option on re-exposure and that the steroid dose should be stratified according to the severity of the previous reaction. However, the benefit of adding H2 antihistamines is not sufficiently demonstrated, and they are not routinely administered.59-61 Moreover, corticosteroid premedication has been discussed to be associated with substantial costs and indirect harm related to length-of-stay prolongation in in-patients.52

The minimal interval for premedication administration is unknown. A 12-hours or 13-hours oral scheme of corticosteroids is usually recommended but an accelerated intravenous scheme is proposed when the multidose schedule is not feasible.54,55

Premedication has not been considered sufficient and might not even be indicated in patients with a history of true IgE-mediated ICM anaphylaxis.55,63,64 Lee et al observed 6/9 selected high-risk patients to be ST positive,54 and Marshall et al observed 2/10 positive DPTs,60 indicating a subgroup of type I allergic patients.

Currently, some American and European associations suggest changing ICM within the same class of low-osmolar ICM.58,65 Several recent studies have demonstrated that changing ICM in mild reactions to low-osmolar ICM reduced the rate of breakthrough reactions.54,66,67 Some authors found that changing the ICM was more effective than premedication in prevention of recurrence reactions.66 Others found that the recurrence rate of mild IHR was 31.1% when patients were re-exposed to the same ICM without premedication.67 When the ICM was changed, the recurrence rate of IHR was 12%, and with the addition of antihistamine premedication, the rate was 7.6%.

3.5.2 | Practical statements

Some American associations advise premedication for all patients with an "allergic-like" or unknown-type contrast reaction.57 However, European guidelines recently removed the suggestion of invariably using premedication in patients at risk and emphasized the need to undergo an allergy evaluation to confirm or exclude an IgE-mediated drug allergy to ICM and to identify safe alternatives. They advised to change the ICM when it is known, since the use of an alternative ICM has proven more helpful in reducing the rate of recurrent IHR to ICM.54,66 If the culprit ICM is unknown and there is an urgent need for ICM, premedication with H1 antihistamines and corticosteroids may prevent recurrence in mild-to-moderate immediate reactions.5,54,66

In patients with a history of a prior severe reaction, re-administration of ICM is a relative contraindication, but if necessary and in the absence of alternatives, premedication should be considered, although evidence for efficacy is lacking in high-risk patients. In patients with a history of moderate-to-severe reaction, a higher dose of corticosteroids than usually used could be considered.54

3.6 | How should a patient be evaluated?

3.6.1 | Background

Patients with a history of an IHR to ICM may react again upon renewed administration of ICM.52 But in cases reporting a mild ICM-induced IHR limited to the skin, the risk of developing
**3.6.2 | Practical statement**

The most important step in the evaluation of an IHR to ICM is a thorough history in order to establish the severity of the reaction. An isolated urticarial skin reaction represents a mild IHR, and anaphylactic shock is the most severe form. Allergy work-up for (presumably IgE-mediated) immediate-type, allergic ICM hypersensitivity includes SPT undiluted, IDT with a dilution of at least 1:10 (highest sensitivity), BAT (facultative), and DPT (if needed). Unfortunately, at present only a minority of patients with ICM-induced IHR undergoes allergy testing, and therefore, in many patients, ICM are re-administered without prior testing.

Moreover, in clinical practice the culprit ICM is often unknown, as documentation in radiology and cardiology departments is often restricted to the total volume of the injected ICM, whereas the exact name of the ICM is not always mentioned. Premedication with H₁ antihistamines and corticosteroids may prevent recurrence in mild-to-moderate immediate reactions.⁵⁻⁶ However, as premedication has not been shown beneficial in moderate/severe IHR and corticosteroids might induce substantial side effects, its use is becoming more and more controversial and applying an alternative skin test-negative ICM without premedication is a valid option and may perhaps become the standard in the future, after more experience is being generated.⁵⁵

### 4 | NONIMMEDIATE HYPERSENSITIVITY REACTIONS

NIHR to ICM range from unspecific and toxic symptoms (such as local pain or local wheal at the injection site, generalized pruritus, transient erythema, dizziness, nausea) to severe cutaneous adverse reactions. These latter reactions are mainly T-cell-mediated, in skin biopsies a perivascular infiltrate of CD₄⁺ and CD₈⁺ T cells has been uniformly demonstrated, and positive delayed STs are common. Recently, it has been demonstrated that DRESS syndrome due to ICM occurs with a very short delay, within the week following the ICM injection.⁶⁸ Positive lymphocyte transformation...
Recommendations (Figure 1)

- All patients with ICM-induced IHR should undergo allergy testing in order to diagnose or exclude ICM allergy and to identify a safe ICM alternative (strong/low).
- If STs are negative there is no evidence for an ICM allergy, rather for a nonallergic ICM hypersensitivity, which is mostly mild to moderate in severity. The options are to give an alternative ICM or to perform a DPT to confirm tolerability.
- As an approach for patients with a convincing history of ICM-induced IHR (no allergy testing yet), in which ICM-based radiological imaging is urgently needed, these steps can be followed:
  a. If IHR is limited to the skin, that is, urticaria with or without angioedema: ICM can be administered after premedication (moderate/low). If the culprit ICM is known, an alternative ICM should be used.
  b. Moderate-to-severe IHR (full-blown anaphylaxis): Omit ICM and perform native computed tomography (CT) or magnetic resonance (MR) scan instead; if ICM is indispensable, administer the ICM after premedication and in anesthesia stand-by (strong/low). If the culprit ICM is known, an alternative ICM should be used (strong/high).

4.1 | What are the indications for testing?

4.1.1 | Background

As for IHR, NIHR to ICM may vary from uncomplicated MPE to complex hypersensitivity reactions such as DRESS or severe and life-threatening bullous drug reactions such as SJS/TEN. The most frequent clinical manifestation is mild-to-moderate MPE. A history of a previous ICM-induced adverse reaction is a predisposing factor for NIHR.

4.2 | How to perform skin testing?

4.2.1 | Background

An immunological, T–cell-mediated mechanism has been demonstrated for the various clinical manifestations of NIHR by delayed reading IDT and patch test (PT), immune-histological findings, and specific proliferation of T cells in vitro. STs can be helpful to identify the responsible ICM and to find alternative ICM. In a European multicenter study, 98 patients with NIHR to ICM were investigated by SPT, IDT, and PT using the suspected culprit and a variety of other ICM of all four chemical subgroups. STs with delayed reading were positive in 38/98 patients (38%, 95% CI 28%-47%), with 32% being positive in the IDT with late reading, 28% in the PT, and only 3% in the SPT with delayed reading, some patients tested positive in only one test. A meta-analysis on STs in hypersensitivity reactions to ICM found the overall positive rate for STs in NIHR to be 26% (95% CI, 15%-41%), for SPT 7% (95% CI, 1%-30%), for IDT 22% (95% CI, 13%-34%), and for PT 16% (95% CI, 9%-26%), and an added value if IDT and PT were combined and the suspected culprit was included. No false-positive STs were found in six European studies on NIHRs. If four or more ICM were tested, ST-negative ICM were detectable in 90% of cases (95% CI 77%-96%). IDT performed between 1 and 6 months after the resolution of the hypersensitivity reactions showed higher positive rates (48%) than if later performed (23%, P = .02). IDTs are generally carried out at 1:10 dilutions for IHR and NIHR, but up to 70% of IDT reacted to the undiluted ICM with good safety without generating false-positive IDT, and it may be used if the immediate reading of the 1:10 dilution is negative. For SCARs, however, where very little information on ST is available, it is not advisable to proceed directly to undiluted ICM in IDT, and a
safe stepwise approach starting with PT, followed by IDT 1:10, and finally IDT 1:1 in which for each step delayed reading is performed prior to proceeding to the next step, should be considered.

Regarding the NPV of STs, whereas two older smaller studies had reported a lower NPV,\textsuperscript{69,72} a meta-analysis and larger studies performed afterward highlighted the usefulness of STs for identifying safe alternatives,\textsuperscript{21,29,77} and a NPV of 86.1% (IC95%: 72.1%-94.7%) has been calculated in the largest study.\textsuperscript{71} Milder flare-up reactions upon IDT in NIHR seem to be rare, but possible.\textsuperscript{72}

4.2.2 | Practical statement

For IDT, 1:10 dilutions of the standard ICM solution are nonirritative.\textsuperscript{5} However, the sensitivity of IDT with delayed reading in NIHR seems to be higher if undiluted ICM concentrations are used.\textsuperscript{69} In that case, the frequent difficulty to interpret immediate reaction needs to be ignored as it does not represent a sign of an immediate IgE-mediated allergy. IDT with undiluted ICM may induce irritative large uncolored wheals after 20 minutes without surrounding erythema, possibly due to the osmolarity of the products, which may be difficult to distinguish from a positive IDT (large wheal with a surrounding erythema). IDTs should ideally include a first reading after 48 hours and a second one after 72 hours.\textsuperscript{6} For PT, ICM can be tested undiluted. PTs should have two readings: at the moment of removal (after 48 hours) and a delayed reading 72-120 hours later.\textsuperscript{6} Due to the possibility of later appearance of skin reactions, patients should be instructed to report any skin reaction at the test site.

### Recommendations

- **When to test:** ideally within the first 6 months after the clinical reaction and more than 6 months in case of DRESS (weak/low).
- **What to test:** ideally the suspected culprit and several commonly used alternatives due to the extended cross-reactivity in NIHR (strong/moderate). In DRESS and FDE, patch tests can be useful and SPT and IDT should not be used (weak/low).
- **How to test:** IDT with 1:10 dilution of the standard concentration of ICM or undiluted on the upper arm or upper back with delayed reading after 48 and 72 hours (weak/low). PT on the upper back with undiluted standard solution of ICM with reading at 48 hours and a delayed reading (72-120 hours) (strong/low). Patients should be instructed to return for additional readings in case of any later appearing skin reaction at the test site (weak/low). Using both tests may enhance sensitivity (weak/low). If all tests are negative: Consider IDT and/or PT with undiluted ICM in local testing, especially in FDE (weak/low).

Some patients with FDE or SDRIFE might exhibit negative STs, if tested only on the upper arms or upper back. In FDE, testing should be done at the previous involved area by in situ PT.\textsuperscript{78} A potential explanation could be the presence of drug-specific resident memory T cells at the site of the clinical reaction, which seem to be more reactive upon local challenge (skin testing) than central memory T cells.\textsuperscript{79}

Allergological work-up should be ideally performed within 6 months after the clinical reaction since sensitivity of the tests is reduced thereafter.\textsuperscript{69}

4.3 | What is the value of the Lymphocyte Transformation Test?

4.3.1 | Background

LTT measures the proliferation of T cells after stimulation with a drug in vitro. It aims to detect circulating drug-specific memory T cells, which proliferate upon drug stimulation. In most cases, proliferation is measured as \(^{3}\text{H}\text{-thymidine uptake as counts per minutes (cpm).}\) Generally, results are given as stimulation index in relation to unstimulated cells. The sensitivity and specificity of the LTT must be newly defined for each antigen. It has been used to demonstrate specific recognition of ICM by T lymphocytes in patients with NIHR.\textsuperscript{73,74}

LTT results in NIHR to ICM are heterogeneous, and the sensitivity ranges from 13% to 75%, variability probably related to the number of patients studied, their clinical characteristics, the diagnostic approach used, and the expertise of the diagnostic laboratory.\textsuperscript{80} LTT can only be considered as an additional tool and taking into account that a negative LTT cannot rule out a NIHR.\textsuperscript{5}

4.3.2 | Practical statement

LTT is not recommended at the acute stage, but rather after 4-8 weeks after remission\textsuperscript{81} and within 2-3 years after the reaction.\textsuperscript{82} Corticosteroids in doses higher than 0.2 mg/kg body weight prednisolone equivalent and other immunosuppressive or immunomodulatory agents may interfere with the test. A NPV for LTT in NIHR to ICM is not available. As radioactive materials have been banned in many laboratories, the use of “modified nonradioactive LTT” will be a better choice.

### Recommendations

- The LTT can be done as an additional diagnostic tool in selected cases with contraindications for STs (weak/low).
- It should only be performed by experienced physicians (weak/low).
4.4 | Is there a role for DPT?

4.4.1 | Background

DPT with ICM can be necessary to rule out the diagnosis and to identify alternative ICM that can be used in subsequent radiological examinations, if hypersensitivity to ICM is confirmed.\(^5,6,26,46,69,72,83\) The ICM chosen for DPT will depend on ST results and reaction severity. The polyvalent reactivity seems higher in NIHR than in IHR.\(^6,13,21,37,69,74,80\) The most frequently association has been found between iodixanol and iohexol\(^6,37,69\) and between ioversol and iomeprol.\(^2\)

4.4.2 | Practical statement

DPT with the culprit ICM may rule out the diagnosis of NIHR in patients with nonsevere reactions and with an alternative in patients with confirmed NIHR or with severe reactions.\(^3\) It has been reported that DPT identified NIHR to ICM in up to 41.7%-56.4% of negative ST patients.\(^69,72\) It has been reported that iobitridol shows low cross-reactivity in patients with NIHR to other ICM.\(^76\)

Several modalities of DPT with ICM have been reported with no consensus regarding the total dose or intervals of DPT, for example: (a) increasing doses at 1-hours intervals in two runs separate by 1 week (5-10-15 mL on the first day and 20-30-50 mL (cumulative dose: 100 cc) on the second day)\(^76\); (b) 5-20 mL of iobitridol at 1-hour interval and two 50 mL doses at 1-hour interval (cumulative dose: 100 mL) the following week\(^76\); (c) 1/100 of the dose required for radiological examination and 1-24 hours later 1/10 of the dose required\(^76\); and (d) 0.05-0.5-1-5-10 mL at 30-minutes interval.\(^13,51\) In patients with NIHR, premedication is not effective.\(^84,85\)

4.5 | When is premedication recommended?

4.5.1 | Background

No studies have systematically evaluated the use of premedication for prevention or recurrences of NIHR. Although it has been indicated that corticosteroids premedication in patients with previous NIHR to ICM may be useful,\(^37\) repeated reactions, including a case of TEN, have been described.\(^3,84,86,87\)

4.5.2 | Practical statements

There is no evidence for a premedication in patients with NIHR, and this can be especially harmful in patients with a history of a severe NIHR (eg, TEN, DRESS).

Recommendation

- There is no evidence to prove the efficacy of premedication in patients with NIHR to ICM (high/strong).

Recommendations

- DPT with ICM can be necessary to confirm the diagnosis or to identify a safe alternative ICM (weak/low).
- The ICM chosen for DPT may be the culprit in patients with nonsevere reactions and negative ST, and a ST-negative alternative in patients with confirmed NIHR or with severe reactions (weak/low).
- Renal function need to be carefully monitored (strong/high).
- Available protocols should be standardized (strong/high).

4.6 | How should a patient be evaluated

4.6.1 | Background

MPE developing several (mostly 6-12) hours after administration seems to account for the great majority of NIHR.\(^6,69,86\) An exanthematous skin eruption is classified as uncomplicated MPE if signs of a systemic reaction such as fever, hepatitis, or nephritis are virtually absent. In addition, single cases of FDE, flexural exanthema, AGEP, and even life-threatening DRESS, SJS, and TEN have been described as ICM-induced NIHR.\(^3,7,80\)

Recommendations (Figure 2)

- The first and most important step in the evaluation of patients with suspected ICM-induced NIHR is a thorough history (high/strong).
- An uncomplicated MPE should be clearly separated from other clinical reaction patterns (high/strong).
- If there are hints in history or medical documents suggesting a morphologically unusual skin eruption, a systemic reaction including hepatitis or nephritis, or a bullous skin reaction with mucosal involvement, diagnostic testing (ST and DPT) must be based on individual risk-benefit considerations or is even contraindicated (high/strong).
- The evaluation of patients with ICM-associated MPE should include IDT and PT ensuring that patients with allergic ICM hypersensitivity are not missed (low/strong).
- Moreover, skin testing may identify alternative ICM, which are tolerated in DPT and in future radiological investigations (low/strong).
- If clinical history, information from treating physicians, caregivers, or medical records unambiguously indicate an uncomplicated MPE and there is an urgent diagnostic need, ICM may be administered based on individual risk-benefit considerations (low/weak).
4.6.2 | Practical statement

In ICM-related MPE, allergy testing is mandatory to reliably confirm or exclude ICM as cause of the skin rash. It should be borne in mind that only few patients with MPE show a positive test result. Otherwise, many patients may be unjustified labeled as ICM allergic. In nonsevere MPE, the moderate sensitivity and high specificity of STs (performed within 6 months after the clinical reaction) for diagnosis of allergic NIHR in combination with a limited risk (reoccurrence of a MPE) imply that diagnostic DPT is often not necessary. In patients sensitized to several ICM, DPT may be advisable to prove that a certain ST-negative ICM is definitely tolerated.\(^{69}\)

5 | OPEN QUESTIONS FOR IMMEDIATE AND NONIMMEDIATE REACTIONS

5.1 | Is there any cross-reactivity among ICM?

Currently, it is not clear whether “cross-reactivity” does exist or not and further studies are needed. In clinical studies, multiple reactions are regularly observed, in 67% of the 97 patients having at least one positive ST with ICM, STs and re-administration of other ICM may induce reaction.\(^{37}\) In studies with smaller populations, it varies a lot: from 20% \((n = 15)\),\(^{88}\) 26% \((n = 15)\),\(^{72}\) 27% \((n = 22)\),\(^{69}\) 43% \((n = 80)\)\(^{21}\) to 75% \((n = 36)\).\(^{6}\) Cross-reactivity is neither related to iodine, nor to excipients contained in ICM, nor to their ionicity. In NIHR, cross-reactions could be related to the presence of the carbamoyl side chain in some ICM. Hasdenteufel et al.\(^{75}\) reported that only 2 of 22 patients sensitized to ioxiflanol also reacted to iobitridol. In NIHR, Gracia-Bara et al.\(^{89}\) also observed a very few numbers of reactions between iobitridol and other ICM. Preferential multiple reactions are summarized in Table 2.

5.2 | What else in the management?

Radiologists should be prepared to recognize and treat the various types of adverse reactions to ICM, including anaphylaxis. In a retrospective analysis of radiologist practice over a five-year period, adrenaline was only used in 9 out of 457 000 cases, being laryngeal edema the most frequent symptom \((N = 6)\).\(^{90}\) Only 41% of radiologists gave the correct treatment of adrenaline to an IHR.\(^{91}\) Similar studies indicated lacking radiology resident preparedness for pediatric life-threatening events.\(^{92}\) Thus, radiologists’ use of adrenaline

*FIGURE 2 Algorithm for diagnosis and management of non-immediate hypersensitivity reactions to ICM

- AGEP, acute generalized exanthematous pustulosis
- DRESS, drug reaction with eosinophilia and systemic symptoms
- LTT, lymphocyte transformation test
- SJS, Stevens-Johnson syndrome
- TEN, toxic epidermal necrolysis
- or rarely, delayed urticaria and/or angioedema
should be improved by training. Computerized guidelines for the detection and management of patients with ICM hypersensitivity reactions have proven to be effective not only in gaining epidemiological data, but also in standardizing the management and reducing adverse events in patients with previous ICM hypersensitivity reactions.93,94

There has been a concern that IHR to ICM might be more common in systemic mastocytosis (SM), as patients with SM frequently develop anaphylaxis to several triggers.95,96 However, there is no evidence that there is a greater risk of IHR to ICMs in patients with SM compared with the general population. Only few individual cases with IHR to ICMs have also been described in patients with SM, and SM has not ever been reported as an underlying disease in patients with fatal RCM-induced anaphylaxis.97 Nevertheless, in all patients with previous anaphylaxis to ICM, baseline serum tryptase should be determined to screen for mastocytosis. Additionally, patients with SM should also undergo allergy testing to ICMs. Before administering ICMs to adults with mastocytosis, emergency preparedness is necessary and resuscitation facilities should be nearby.

6 | CONCLUSIONS

Hypersensitivity reactions to ICM are still a challenge. It is pivotal to have a good clinical history, but also to evaluate the medical record for discordances, uneventful re-expositions that might help the choice for a safe ICM. STs are recommended to identify patients with IgE- or T–cell-mediated reactions to ICM and to provide guidance on tolerability of alternatives. BAT can be an additional tool for diagnosing patients with IHR with severe reactions or those with high risk. LTT for NIHR may be an alternative when STs cannot be performed. DPT is the gold standard but the decision for performing it needs to be taken based on a risk-benefit analysis of each patient and should be done only in well-equipped centers and by trained personnel. There is no evidence of the efficacy of premedication in patients with severe IHR, IgE-mediated reactions, and NIHR to ICM. Further studies are needed to better understand multiple reactions against ICM. Allergist should convince patients and physicians of the usefulness of critically evaluating the ICM allergy label(s) early on.

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**TABLE 2** Data on reported cross-reactivity of ICM in NIHR (adapted from ref 37)

<table>
<thead>
<tr>
<th>Group A Without carbamoyl chain</th>
<th>Reported cross reactivities between molecules and references</th>
</tr>
</thead>
<tbody>
<tr>
<td>loxithalamate (IM)</td>
<td>HF of CR with iohexol (iodixanol is the dimer of iohexol)6,37,69,72</td>
</tr>
<tr>
<td>With carbamoyl chain</td>
<td>HF of CR with iomeprol and ioversol6</td>
</tr>
<tr>
<td>iodixanol (NID)</td>
<td>HF of CR with iohexol (iodixanol is the dimer of iohexol)6,39,68,72</td>
</tr>
<tr>
<td>lohexol (NIM)</td>
<td>HF of CR with iohexol and ioversol6</td>
</tr>
<tr>
<td>ioversol (NIM)</td>
<td>HF of CR with iohexol, iohexol and iomeprol6</td>
</tr>
<tr>
<td>Iomeprol (NIM)</td>
<td>HF of CR with iohexol, iohexol and ioversol6</td>
</tr>
<tr>
<td>Iopamidol (NIM)</td>
<td>HF of CR with iomeprol6</td>
</tr>
<tr>
<td>Iopromide (NIM)</td>
<td>Less investigated, HF of CR with iomeprol21</td>
</tr>
</tbody>
</table>

**Group B**
- Iobitridol (NIM)
- Ioxaglate (ID)

**Group C**
- Amidotrizoate (IM)

Abbreviations: IM, ionic tri-iodized monomer; NIM, nonionic tri-iodized monomer; ID, ionic hexa-iodized dimer; NID, nonionic hexa-iodized dimer; HF, high frequency; CR, cross-reactivity; LF, Low frequency.

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**Recommendations**

- Radiologists should improve emergency awareness and training on emergency treatment of ICM IHR (high/strong).
- In all patients with previous anaphylaxis to ICM, baseline serum tryptase should be determined to screen for mastocytosis (low/weak).
- Emergency preparedness is needed before administering ICMs to adults with mastocytosis, and resuscitation facilities should be nearby (low/weak).
CONFLICT OF INTEREST
None of the authors has any conflict of interest.

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