Practice Parameters for Diagnosing and Managing Iodinated Contrast Media Hypersensitivity

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Abstract

Immediate and non-immediate hypersensitivity reactions to iodinated contrast media (ICM) have been reported to occur in a frequency of about 0.5-3% of patients receiving non-ionic ICM. The diagnosis and management of these patients is controversial 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 non-immediate hypersensitivity reactions; besides, they may also help guide on tolerability of alternatives. Drug provocation test is the gold-standard; although, as it is a risky procedure, the decision for performing it needs to be taken based on a risk-benefit analysis. Another source of controversy is the role of in vitro tests for diagnosis and pretreatment for preventing reactions.

INTRODUCTION

Adverse events after iodinated contrast media (ICM) administration may be either hypersensitivity reactions (type B reactions) or toxic reactions (type A reactions) [1, 2]. According to the time interval between ICM application and appearance of symptoms, hypersensitivity reactions are divided into immediate reactions (IHR), which occur within 1 to 6 h after ICM administration, or non-immediate reactions (NIHR), appearing

1

more than 6 h after ICM exposure [2-5]. Both IHR and NIHR have been reported to occur in a frequency of about 0.5-3% of patients receiving non-ionic ICM [3].

IHR induce anaphylaxis, urticaria, angioedema, sometimes together with vomiting, abdominal pain, diarrhea, or more severe reactions affecting the respiratory and cardiovascular systems presenting with dyspnoea, bronchospasm and/or a sudden drop in blood pressure [2-7]. Hypotension may be associated with loss of consciousness (anaphylactic shock). In about 70% of these reactions, the onset is within 5 min after injections [8].

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) [2, 3, 5-7, 9]. In addition, delayed appearing urticaria or angioedema may occur, especially within the first 6 hours after ICM application.

The management of patients with previous hypersensitivity reactions to ICM is controversial among guidelines published by various national and international scientific societies, with recommendations ranging from avoidance or premedication to drug provocation test (DPT) [3, 10, 11] (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 [3].

METHODS

This position paper was commissioned by the European Academy of Allergy and Clinical Immunology (EAACI). It is based on evidences as well as 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 hypersensitivity, 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 [12]. 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.

IMMEDIATE HYPERSENSITIVITY REACTIONS

The mechanism underlying IHRs to ICM is still a matter of controversy [6] and, although in the majority of patients the mechanism is non-allergic, in some cases IgE-mediated allergic reactions are reported [6, 13-16]. The presence of positive skin tests (ST) and basophil activation tests (BAT), and older studies reporting detection of low levels of specific IgE to ionic ICM indicate an IgE-mediated mechanism [6, 13-16]. Histamine and tryptase serum levels [15, 17], as well as the frequency of positive allergy diagnostic tests, increase with the severity of the reaction [6, 10, 11, 13-15, 17, 18]. A recent multicentre 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 [18]. 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 [18]. In contrast, non-allergic reactions are likely when only one organ is affected [18, 19].

IHRs in the context of a contrast-enhanced image-guided procedure are in most cases (74%) contrast media-induced reactions [20]. In the remaining 26%, other culprit substances/cases such as latex, adenosine, or

vasovagal reaction could be identified [20].

1.- What are indications for testing?

a) 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) [21] have shown inconsistent results and therefore cannot be used as pre-requisite for performing ICM allergy work-up. Prophetic allergy testing did not show sufficient specificity to be of value due to the high number of patients tested.

b) Practical statement: Allergy testing is indicated in patients with history of IHR. There are no indications for testing patients labelled as "iodine allergy" (povidone iodine, crustaceans, and mollusk) as well as patients with food, respiratory, cutaneous, 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.

Recommendations

- To perform allergic work-up in patients with a history of anaphylaxis

(strong/moderate).

- To perform it in patients with a history of isolated urticaria, angioedema, or bronchospasm *(weak/low).*

2.- How to perform skin testing?

a) Background: IHRs to ICM have traditionally been perceived as non-allergic reactions [22], therefore ST has been considered as an inappropriate tool for the diagnosis of such reactions, although this view has changed by newer evidence [5, 6, 14, 23-26]. The sensitivity of STs in IHR varies from 4.2% to 73% among different studies [6, 13, 24, 27, 28]]. 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 the largest study to date, 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, 30]. Negative predictive value (NPV) of ST with ICM has been reported to range from 96.6% to 37.5% [19, 24, 29, 31-34]. A French study reported high NPV of skin testing for ICM (94.2% (95% CI 89.6% to 97.2%) for IHR) [19]. On the contrary, a Spanish study reported that only 62.5% of their patients were diagnosed by ST and 37.5% by drug provocation test (DPT) [24]. In the same centre, NPV were 97.3% or 80% when DPT was done by injecting 10 mL or 50 mL, respectively [34].

Such high variability may be due to patient selection, different concentrations used for ST and injected volume for DPT, the clinical symptoms of the patients, their severity, the ICM substance used, and the time between the reaction and the study [32, 35, 36]. 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 is the limited duration of skin reactivity due to IgE clearance [37].

b) Practical Statement: SPT and IDT should be performed according to EAACI Guidelines [38]. ICM should be used undiluted at 300-320 mg/ml for SPT and diluted 1:10 for IDT [5, 6]. It has been reported that patients with severe reactions developed systemic reactions after IDT, therefore in these cases it is recommended to start with higher dilutions [6, 32]. STs should be performed with the ICM involved in the reaction, if known [5, 10], as it has been reported that 56.7% [39] to 86% of patients with positive STs gave positive results to the culprit [6]. 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.- 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 during the acute phase of the reaction, and BAT for identifying the ICM involved in the reaction once the reaction has resolved.

3.1. Histamine, tryptase, and cysteinyl leukotrienes

a) 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 [17, 40]. Tryptase is continually secreted by mast cells in tissues, and then it diffuses into the circulation, where it can be measured as protryptase, which 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 [41

b) 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 h of the event) and baseline total tryptase levels (at least 24 h after all signs and symptoms of the event have subsided) to distinguish between an increased mast cell burden (*e.g.* , 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 × baseline tryptase level] [42] or at least 20% above baseline plus 2 ng/mL during or within 4 h after a symptomatic period [43]. 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, 18, 44].

Recommendation

- Tryptase determination is useful for confirming IHR to ICM, if an increase is detectable (strong /moderate).

3.2. Basophil activation tests

a) 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, 45]. Regarding ICM, three studies demonstrate a BAT sensitivity of 46-63% depending on the threshold chosen, and a specificity of 89-100% [13, 25, 46].

b) Practical Statement: BAT can be a complementary tool to diagnose IHR to ICM [5], showing good correlation with ST and DPT results [24]. 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 [24]. However, the NPV has not been clearly determined [47].

Recommendation

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

4.- Is there a role for Drug Provocation Test?

4

a) 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 [9, 19, 24, 30-33, 39]. In the American Guidelines there is no statement favouring DPT with ICM in IHRs [48]. Studies from Japan indicated severe reactions to very small "pre-test 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, 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 centres [9, 24, 32].

Application of ICM is potentially harmful. Besides hypersensitivity reactions, they 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.

b) Practical Statement: DPT can be done either if the ST with the culprit is negative to confirm a diagnosis, to confirm tolerance to a ST-negative alternative in patients with positive ST to ICM, or with an anaphylactic reaction in which DPT with 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 renal complaints (eGFR$<$45 ml/min/1.73m^2), 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 application 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 breast-feeding women should be excluded from DPT. Metformin medication should be stopped 24h 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 low-osmolality or isosmolar RCM, check renal function before injection, and consider intravenous saline solution (0.9%) [25].

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: (i) 5-15-30-50 mL (cumulative dose = 100 mL) at 45-min intervals [24]; (ii) 0.05-0.5-1-5-7.5-10-25 mL (cumulative dose = 49.05 mL) at 30-min intervals [51].

Recommendations

- 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 need to be taken based on a risk-benefit analysis of each patient and should be done only in well-equipped centres and by trained personnel in immediate emergency treatment (strong /low).

- DPT is not indicated in patients at risk (renal complaints, hyperthyroidism, radioactive iodine therapy, pregnant and breast-feeding women, nephrotoxic medication, etc.) (strong/high).

5.- How should a patient be evaluated?

a) 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 moderate to severe anaphylaxis after re-administration of ICM is below 1% [53].

5

b) *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, 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 undergo 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 departments is restricted to the total volume of the injected ICM, whereas the exact name of the ICM is not always mentioned.

Recommendations (Fig 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 non-allergic ICM hypersensitivity, which is mostly mild to moderate in severity. The options are to give an alternative ICM with premedication 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:

(i) If IHR is limited to the skin, i.e. urticaria with or without angioedema: ICM can be administered after pre-medication (*high/strong*). If the culprit ICM is known, an alternative ICM should be used.

(ii) 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 pre-medication and in anaesthesia stand-by (*low/strong*). If the culprit ICM is known, an alternative ICM should be used.

6.- When is premedication recommended?

a) *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 (e.g. prednisone 13 h, 7 h and 1 h prior to ICM exposure with diphenhydramine 1 h prior to ICM exposure) [54-56]. Lee et al. [57] 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 [58-60]. Moreover, corticosteroid premedication has been discussed to be associated with substantial costs and indirect harm related to length-of-stay prolongation in in-patients [61].

The minimal interval for premedication administration is unknown. A 12-h or 13-h oral scheme of corticosteroids is usually recommended but an accelerated intravenous scheme is proposed when the multidose

schedule is not feasible [54, 55]. Recently, a 5-h scheme was proposed to be non-inferior to the 13-h scheme [62], although this is not feasible under routine conditions in radiology clinics/units.

Premedication has not been considered sufficient and might not even be indicated in patients with a history of true IgE-mediated ICM anaphylaxis [63, 64]. Lee et al. observed 6/9 selected high-risk patients to be ST positive [57], and Marshall et al. observed 2/10 positive DPTs [59], 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 [55, 56]. Several recent studies have demonstrated that changing ICM in mild reactions to low-osmolar ICM reduced the rate of breakthrough reactions [57, 65, 66]. Some authors found that changing the ICM was more effective than premedication in prevention of recurrence reactions [65]. Others found that the recurrence rate of mild IHR was 31.1% when patients were re-exposed to the same ICM without premedication [66]. When the ICM was changed, the recurrence rate of IHR was 12% and with the addition of antihistamine premedication the rate was 7.6%.

b) *Practical Statements:* Some American associations advise premedication for all patients with an "allergic-like" or unknown-type contrast reaction [55]. However, European [56] 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 [53, 54]. 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, 57].

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 [57].

Recommendation- Premedication is not a general recommended approach (*high/strong*). - In cases the culprit ICM is unknown and ICM administration is needed premedication could be an option (weak /low).

NON-IMMEDIATE 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 RCM occurs with a very short delay, within the week following the RCM injection [67]. Positive lymphocyte transformation tests (LTT) and ICM-specific T-cell clones have been demonstrated in some patients [68]. The immunological reaction in patients with NIHR is directed against the structure of the ICM and not against the iodine ion in the vast majority of patients. NIHR to ICM are characterized by a T-cell mediated mechanism, appearing from hours to days after administration of the ICM. Delayed appearing non-allergic urticaria and/or angioedema occurring > 6 hours after ICM administration seem to be caused by a different, poorly understood mechanism.

Non-ionic dimeric ICM induce significantly more often cutaneous NIHRs than non-ionic monomeric ICM [69]. In fact, more than 50% of MPE are induced by the non-ionic dimeric ICM iodixanol [70].

1.- What are the indications for testing?

a) 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 [3, 9, 19, 23, 39, 68]. A history of a previous ICM-induced adverse reaction is a predisposing factor for NIHR.

b) Practical statement: Allergy testing is indicated in patients with clinical history indicative of MPE, FDE, SDRIFE, or AGEP. In severe bullous skin reactions and in DRESS, ST is recommended, whereas DPT is generally contraindicated, although even in these cases exceptions are possible depending on the risk of a renewed severe reaction and urgent need. Although the mechanisms underlying delayed-appearing urticaria and angioedema are not well understood, they should be studied.

Recommendations

- To identify patients with T cell-mediated reactions to ICM and to provide guidance on tolerability of alternatives, all patients with a suspicion of ICM-induced exanthema should be tested (strong/moderate).

- Delayed-appearing urticaria and angioedema are usually ST-negative (weak /low).

2.- How to perform skin testing?

a) 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* [6, 71-74]. STs can be helpful to identify the responsible ICM and to find alternative ICM [3, 5, 6, 19, 28, 31, 39, 68, 71, 75, 76]. In a European multicentre 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 [6]. 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 [29]. 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%) [29]. 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=0.02) [6]. 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 1:10 dilution is negative [68].

Regarding the NPV of STs, a Korean study highlights the usefulness of STs for identifying safe alternatives [77]. However, Vernassiere et al. reported that DPT were positive in 41.7% of patients with negative ST [71], similarly to Torres et al [68], who found 32.3% of patients to have a positive DPT with a ST-negative ICM – both demonstrating low NPV of ST in NIHR to ICM in their patients. Milder flare-up reactions upon IDT in NIHR seem to be rare, but possible [71].

b) Practical Statement: For IDT, 1:10 dilutions of the standard ICM solution are non-irritative [5]. However, the sensitivity of IDT with delayed reading in NIHR seems to be higher if undiluted ICM concentrations are used [68]. 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 RCM may induce irritative large uncoloured wheals after 20 minutes without surrounding erythema 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 [5]. 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 [5]. Due to the possibility of later appearance of skin reactions, patients should be instructed to report any skin reaction at the test site.

Some patients with MPE and those with FDE or SDRIFE will exhibit negative STs, if tested on the upper arms or upper back. In FDE testing should be done at the previous involved area by *in situ* PT [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 [72].

8

Allergological work-up should be ideally performed within 6 months after the clinical reaction since sensitivity of the tests is reduced thereafter [68], but after 6 months in case of DRESS.

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 (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).

3.- What is the value of the Lymphocyte Transformation Test?

a) 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 (= antigen) stimulation. In most cases, proliferation is measured as ^{3}H-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 [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 [79]. LTT can only be considered as an additional tool and taking into account that a negative LTT cannot rule out a NIHR [5].

b) Practical Statement: LTT is not recommended at the acute stage, but rather after 4–8 weeks after remission [80] and within 2–3 years after the reaction [81]. Corticosteroids in doses higher than 0.2 mg/kg body weight prednisone equivalent and other immunosuppressive or immunomodulatory agents may interfere with the test. A NPV for LTT in NIHR to ICM is not available.

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.- Is there a role for DPT?

a) 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, 25, 31, 68, 71, 82]. The ICM chosen for DPT will depend on ST results and reaction severity. The polyvalent reactivity seems higher in NIHR than in IHR [3, 16, 20, 24, 58, 62, 73, 83]. The most frequently association has been found between iodixanol and iohexol [6, 68, 76], and between ioversol and iomeprol [19].

b) Practical Statement: DPT with the culprit ICM may rule out the diagnosis of NIHR in patients with non-severe reactions, and with an alternative in patients with confirmed NIHR or with severe reactions [5]. It has been reported that DPT identified NIHR to ICM in up to 41.7%-56.4% of negative ST patients [68, 71]. 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, e.g.: (i) increasing doses at 1-h 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) [10]; (ii) 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 [80]; (iii) 1/100 of the dose required for radiological examination and 1–24 h later 1/10 of the dose required [39, 71]; (iv) 0.05-0.5-1-5-7.5-10-25 mL at 30-min interval [51]. In patients with NIHR, premedication is not effective [84, 85].

Recommendation s

- 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 non-severe 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).

5. How should a patient be evaluated

a) Background: MPE developing several (mostly 6-12) hours after administration seems to account for the great majority of NIHR [6, 68, 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 [78, 87].

b) 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 labelled as ICM allergic. In non-severe MPE, the moderate sensitivity and 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) implies 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 [68].

Recommendations (Fig. 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 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*).

6.- When is premedication recommended?

a) Background: There are no specific studies conducted in NIHR to establish the usefulness of premedication in the prevention of recurrences. Although some studies [55] indicated that corticosteroids premedication in patients with previous NIHR to ICM may be useful, repeated reactions, including a case of TEN, have been described [84, 85, 88].

b) 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 (e.g. TEN, DRESS).

Recommendation

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

OPEN QUESTIONS FOR IMMEDIATE AND NON-IMMEDIATE REACTIONS

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 [39]. In studies with smaller populations, it varies a lot: from 20% (n= 15) [89], 26% (n= 15) [71], 27% (n= 22) [68], 43% (n= 80) [19] 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 RCM. Hasdenteufel *et al.* [71] reported that only 2 of 22 patients sensitized to iodixanol also reacted to iobitridol. In NIHR Gracia-Bara et al. [82] also observed a very few numbers of reactions between iobitridol and other ICM. Preferential multiple reactions are summarized in Table 2.

Recommendation:

- Further studies are needed to understand better multiple reactions against ICM (strong /moderate).

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 457000 cases, being laryngeal oedema 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 paediatric life-threatening events [39, 68, 71-74, 77, 83, 86, 92]. Thus, radiologists' use of adrenaline 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 [87, 93].

Recommendations

- Radiologists should improve emergency awareness and training on emergency treatment of ICM IHR (high/strong).

CONCLUSIONS

Hypersensitivity reactions to ICM are still a challenge. 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 bears a lot of severe risks (contrast-induced acute kidney injury including death for example) therefore 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 centres 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.

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11

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Table 1. Management of patients with previous hypersensitivity reaction to ICM

Management	Advantages	Disadvantages	Comment	Ref
Avoidance	Safety	Diagnosis not achieved	To be considered in patients in which other diagnostic options (e.g. magnet resonance tomography) are applicable	[47]
Premedication	Easy	Breakthrough reactions in patients with severe previous reactions False sense of security No evidence for benefit No consensus on standard regime Risk of side effects (corticosteroids) Expense of effort and medication	Is not recommended because there is no enough evidence of its effectiveness Probably not helpful for preventing severe allergic HR Often done in the USA but considered controversial in Europe	[56]

Management	Advantages	Disadvantages	Comment	Ref
Alternative by Clinical History	Easy Reduction of reaction rates	Weak evidence	Use of different ICM more effective compared with premedication Difficult to identify the culprit ICM in clinical records Cross-reactivity may exist	[39, 58, 94]
Alternative by ST-negativity	High negative predictive value Exclusion of ICM highly suspected not to be tolerated Severe anaphylaxis unlikely when a ST-negative ICM is taken	Time consuming Expertise needed Only few patients with IHR will have positive ST More useful in NIHR No prediction for non-severe non-allergic reactions	Increasing evidence Recommended in Europe by allergists	[16, 26, 27, 29, 64, 73, 83]
Alternative by DPT-negativity	Approach when ICM application is needed ICM dose can be titrated	Time consuming Hospitalization necessary Expertise needed also for emergency treatment Risk stratification needed	Increasing evidence that DPT is safe Previously avoided because of severe reactions when radiologists used pretest dosages	[8, 19, 62, 95]

Table 2. Data on reported cross-reactivity of ICM in NIHR (adapted from [78]

Group A	Reported cross reactivities between molecules and references
Without carbamoyl chain: Ioxithalamate (IM)	
With carbamoyl chain: Iodixanol (NID)	HF of CR with iohexol (iodixanol is the dimer of iohexol) [6, 39, 68, 71] HF of CR with iomeprol and ioversol [6]
Iohexol (NIM)	HF of CR with iodixanol (iodixanol is the dimer of iohexol) [6, 39, 68, 71] HF of CR with iomeprol and ioversol [6]
Ioversol (NIM)	HF of CR with iodixanol, iohexol and iomeprol [6] LF of CR with iopamidol [89]
Iomeprol (NIM)	HF of CR with iodixanol, iohexol and ioversol [6] HF of CR with Iopromide [19]
Iopamidol (NIM)	LF of CR with ioversol [89]
Iopromide (NIM)	Less investigated, HF of CR with Iomeprol [19]
Group B	
Iobitridol (NIM)	
Ioxaglate (ID)	

Group A	Reported cross reactivities between molecules and references
Group C Amidotrizoate (IM)	

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

Fig. 1 Algorithm for managing and testing patients reporting **immediate reactions** to iodinated contrast media (ICM).
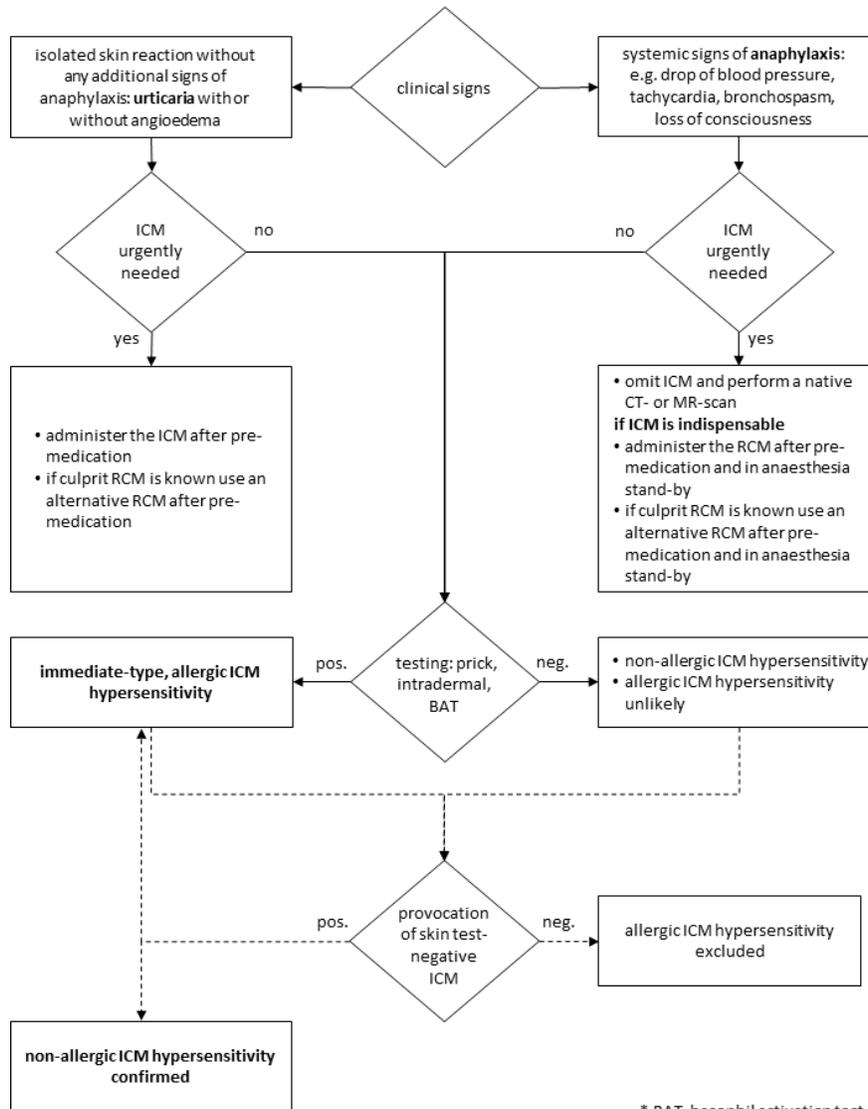
Fig. 2 Algorithm for managing and testing patients reporting **non-immediate reactions** to iodinated contrast media (ICM).

clinical (and laboratory) signs

severe reactions (e.g. AGEP, DRESS, SJS, TEN)*
• RCM urgently needed: omit RCM and perform native CT- or MR-scan
• allergy testing based on risk-benefit consideration

uncomplicated, measles-like, **maculopapular exanthem****

ICM urgently needed

yes → • administer the ICM
• if culprit ICM is known use an alternative ICM

no

testing: intradermal, patch, LTT

pos. → **non-immediate-type, allergic ICM hypersensitivity**

neg. → allergic ICM hypersensitivity unlikely

provocation of skin test-negative ICM

pos.

neg. → allergic ICM hypersensitivity excluded

* 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

20