Clinical Practice Guidelines for Diagnosis and Management of Hypersensitivity Reactions to Contrast Media

Rosado Ingelmo A1, Doña Diaz I2, Cabañas Moreno R3, Moya Quesada MC4, García-Avilés C5, García Nuñez I6, Martínez Tadeo JI7, Mielgo Ballesteros R8, Ortega-Rodríguez N9, Padial Vilchez MA10, Sánchez-Morillas L11, Vila Albelda C1, Moreno Rodilla E12*, Torres Jaén MJ2*

1Unidad de Alergia, Hospital Universitario Fundación Alcorcón, Alcorcón, Madrid, Spain
2Allergy Unit, IBIMA-Regional University Hospital of Málaga, UMA, Málaga, Spain
3Department of Allergy, Hospital La Paz, Health Research Institute (IdiPAZ), Madrid, Spain
4Sección de Alergia CH Torrecárdenas, Almería, Spain
5Unidad de Alergia, Hospital Moncloa, Madrid, Spain
6Servicio de Alergología, Hospital Quirón Málaga, Málaga, Spain
7Servicio de Alergología, Hospital Universitario Ntra Sra de Candelaria, Santa Cruz de Tenerife, Tenerife, Spain
8Servicio de Alergología, Hospital Universitario 12 de Octubre, Madrid, Spain
9Servicio de Alergia, Hospital Universitario de Gran Canaria Dr Negrín, Las Palmas de Gran Canaria, Spain
10Servicio de Alergología, Hospital Infanta Sofía, San Sebastián de los Reyes, Madrid, Spain
11Servicio de Alergología, Hospital Clínico San Carlos, Madrid, Spain
12Servicio de Alergología, Complejo Asistencial Universitario de Salamanca, Salamanca, Spain
*Both authors contributed equally to this study.
On behalf of the Drug Allergy Committee of Spanish Society of Allergy and Clinical Immunology (SEAIC)

Abstract

The objective of these guidelines is to ensure efficient and effective clinical practice. The panel of experts who produced this consensus document developed a research protocol based on a review of the literature.

The prevalence of allergic reactions to iodinated contrast media (ICM) is estimated to be 1:170 000, that is, 0.05%-0.1% of patients undergoing radiologic studies with ICM (more than 75 million examinations per year worldwide). Hypersensitivity reactions can appear within the first hour after administration (immediate reactions) or from more than 1 hour to several days after administration (nonimmediate or delayed reactions). The risk factors for immediate reactions include poorly controlled bronchial asthma, concomitant medication (eg, angiotensin-converting enzyme inhibitors, β-blockers, and proton-pump inhibitors), rapid administration of the ICM, mastocytosis, autoimmune diseases, and viral infections.

The most common symptoms of immediate reactions are erythema and urticaria with or without angioedema, which appear in more than 70% of patients. Maculopapular rash is the most common skin feature of nonimmediate reactions (30%-90%). Skin and in vitro tests should be performed for diagnosis of both immediate and nonimmediate reactions. The ICM to be administered will therefore be chosen depending on the results of these tests, the ICM that induced the reaction (when known), the severity of the reaction, the availability of alternative ICM, and the information available on potential ICM cross-reactivity.

Another type of contrast media, gadolinium derivatives, is used used for magnetic resonance imaging. Although rare, IgE-mediated reactions to gadolinium derivatives have been reported.

Prologue

The objective of these guidelines is to ensure efficient and effective clinical practice in the diagnosis and management of hypersensitivity reactions to radiologic contrast media. The guidelines were developed by a panel of allergy specialists from the Drug Allergy Committee of the Spanish Society of Allergy and Clinical Immunology (SEAIC) with extensive clinical expertise in the evaluation and management of hypersensitivity reactions and broad research experience.

We performed a systematic and independent review of the literature up to November 2015 and established a consensus of expert opinion. We evaluated the applicability of the guidelines in our daily clinical practice. The guidelines were evaluated and criticized by external reviewers with expertise in the field.

Method

The panel of experts who produced this consensus document developed a research protocol outlining the background to the subject of study, the objectives of the study, and the questions and hypotheses from which search criteria were defined.

The main sources used for the literature search included electronic databases and archives (MEDLINE-PubMed, Science Direct, OVID) and a database of systematic reviews (Cochrane Library).

Search criteria were established to facilitate the identification of items relating to definitions, prevalence, classification, clinical manifestations, diagnosis, treatment, and prevention of the various types of reactions to contrast media. The keywords for radiologic contrast media—iodinated, ionic, nonionic, monomeric, dimeric, and gadolinium—were combined with the words allergy, hypersensitivity, anaphylaxis, and immediate and non-immediate reactions.

We selected only original research articles or systematic reviews.

Grades of recommendation were defined according to the Scottish Intercollegiate Guidelines Network [1].

Introduction

Iodinated contrast media (ICM) were introduced into clinical practice in the early twentieth century [2-4]. However, their application was initially limited owing to poor radiopacity and toxicity [5,6]. In the 1950s, ICM were increasingly used thanks to new formulations with higher resolution and lower toxicity. In the 1970s, nonionic dimeric ICM and derivatives with higher physiological osmolality [7] were developed. Nowadays, ICM are administered more than 75 million times per year worldwide [8,9].

Adverse reactions to ICM are not uncommon, but they are usually mild and caused by toxicity or hypersensitivity. Reactions are often underreported, and severe reactions may not always be recorded [10,11]. Hypersensitivity reactions can appear within the first hour after administration (immediate reactions) or more than 1 hour to several days after administration (nonimmediate or delayed reactions) [12]. Immediate reactions have long been attributed to non–IgE-mediated mechanisms [9], although there is growing evidence that tryptase levels increase after the reaction. Furthermore, positive skin test or basophil activation test results could support an IgE-mediated mechanism in some cases [13-17]. The prevalence of nonimmediate hypersensitivity reactions has increased significantly in the last decade, whereas that of immediate reactions has decreased, with the result that nonimmediate reactions are now more frequent than immediate reactions [18]. Nonimmediate reactions can occur at least 1 hour after administration, although they usually appear after 24-48 hours and potentially after even longer periods [19].
significant percentage of reactions to ICM are true allergic reactions requiring careful and adequate management, and in many instances, patients must undergo repeated testing with ICM. Not performing ICM studies could imply more risk than benefit.

Contrast media are also used for magnetic resonance imaging (MRI) to improve the visibility of internal structures. Their application has increased markedly in recent years, with gadolinium derivatives being the most frequent. Although rare, IgE-mediated reactions to MRI contrast media have been reported [20-23].

Classification and Physicochemical Properties of ICM

ICM are iodine salts whose basic chemical structure comprises a benzene ring with at least 3 iodine atoms (triiodobenzene). The number of iodine atoms in each molecule is responsible for producing radiopacity [24]. ICM can be classified as having a monomeric structure if they have a benzene ring or a dimeric structure if the benzoic nucleus is covalently bound. The attachment of structural elements to the benzene ring determines their pharmacological and physicochemical characteristics.

An ICM is ionic if it transforms into ions or charged particles in aqueous solution or nonionic if it does not form ions, remaining instead an electrically neutral particle in solution. The ionization capacity of a given medium is directly related to the frequency and severity of the adverse reaction. ICM can also be classified according to osmolality (the number of particles generated in solution) into high-osmolality ICM (≥1400 mOsm/kg H2O), low-osmolality ICM (500-900 mOsm/kg H2O), and isosmolar ICM (290 mOsm/kg H2O) [25].

The viscosity of ICM is directly associated with the size of the molecule, the iodine concentration, and an increase in the frequency of delayed adverse effects. However, since viscosity decreases with increasing temperature, it can be reduced by heating the ICM to body temperature (37°C) before administration [26].

ICM can be classified into 4 categories based on their capacity for ionization and number of triiodobenzene rings (Figure 1), as follows:

1) Ionic monomers: salts comprising 1 negatively charged triiodinated benzene ring, together with a sodium and/or meglumine as a cation. Ionic monomers have the highest osmolality (>1400 mOsm/kg H2O).

2) Ionic dimers, which consist of 2 triiodobenzene rings, contain a carboxylic radical, and have low osmolality (600 mOsm/kg H2O).

3) Nonionic monomers, which are triiodinated compounds with hydrophilic hydroxyl groups. Nonionic monomers are second-generation agents and have low osmolality (500-850 mOsm/kg H2O).

4) Nonionic dimers, which contain 2 nonionic triiodinated benzene rings. Nonionic dimers have the lowest osmolality of all ICM (290 mOsm/kg H2O).

Epidemiology

The prevalence of allergic reactions to ICM is estimated to be 1:170 000, that is, 0.05%-0.1% of patients undergoing radiologic studies with ICM [27,28]. These percentages are generally higher for ionic ICM (0.16%-12.66%) than for nonionic ICM (0.03%-3%) [28-30].

In the past, high-osmolality ICM were associated with a high incidence of immediate reactions [31,32]. In the 1970s, the introduction of nonionic low-osmolality ICM led to a marked decrease in the incidence of these reactions. The prevalence of nonimmediate reactions, however, has increased in the last decade, to the extent that they are now more common than immediate reactions [18]. This observation gives cause for concern, because, unlike immediate reactions, nonimmediate reactions cannot be well controlled by pretreatment with corticosteroids and antihistamines (see below, Treatment). The most frequent culprits ICM for both immediate and nonimmediate reactions are iomeprol and iodoxanol [16,33].

Reactions to ICM are usually mild to moderate [34]. Mortality is low, ranging from 1 to 3 per 100 000 administrations, for both ionic and nonionic ICM [30,35]. Risk is higher in patients with cardiovascular diseases and in patients with advanced cancer, especially those receiving specific therapies that can potentiate adverse effects (eg, ß-blockers or angiotensin-converting enzyme [ACE] inhibitors). On the other hand, the risk of reactions to ICM in children is lower [36].

The risk factors for hypersensitivity to ICM are not fully established. Table I lists some of the most frequently described risk factors [37-40]. Additional risk factors for immediate reactions that are common to allergic drug reactions include poorly controlled bronchial asthma, concomitant medications (eg, ACE inhibitors, ß-blockers, and proton pump inhibitors), rapid administration of the drug, mastocytosis, autoimmune diseases, and viral infections [10,11,38,41-46].

It is noteworthy that, contrary to popular belief, allergy to mollusks, crustaceans, fish, and iodine from other sources is not a risk factor for the development of hypersensitivity reactions to ICM.
Pathogenesis of Hypersensitivity Reactions to ICM

Similar to hypersensitivity reactions to drugs, reactions to ICM are generally classified into immediate reactions and nonimmediate/delayed reactions [12,47]. The panorama of hypersensitivity reactions to ICM is now more complex than initially thought [48].

Immediate Reactions

The underlying mechanisms of these reactions have been the subject of speculation over the years and were not originally considered to be allergic, but rather anaphylactic or anaphylactoid owing the capacity of former contrast media to induce nonspecific histamine release [49]. However, there is growing evidence that a group of these reactions can be induced by specific immunological mechanisms [14,50,51], a hypothesis that seems increasingly likely with the reporting of cases with immediate positive skin test and basophil activation test results [16].

Immediate Reactions

The skin is the most affected organ in both immediate and nonimmediate reactions. Specific IgE to ioxaglate and ioxithalamate has been determined in the sera of patients who experience immediate reactions to ICM using immunoassay techniques [14,51] and basophil activation tests, as reported for many other drugs [56-58].

Patients who experience hypersensitivity reactions to ICM have increased plasma levels of histamine and tryptase during the reaction [13] that correlate with severity. While these observations do not constitute direct evidence of an IgE-related mechanism, but rather of mast cell activation [14,59], recent studies have also indirectly shown the presence of specific IgE using the basophil activation test [16,17,53].

The finding that some patients react to ICM on their first exposure indicates that a prior sensitization phase is not always necessary. The mechanism may be similar to that involved in anaphylaxis caused by muscle relaxants in individuals who were not previously exposed [60]. The factors that contribute to the high levels of histamine release include genetic variations associated with the metabolism of vasoactive mediators [61].

Nonimmediate Reactions

According to the penicillin model, nonimmediate reactions can occur as soon as 1-2 hours after administration [62,63]. In fact, generalized urticarial reactions mimicking anaphylaxis have been reported with amoxicillin and were first thought to be IgE-like accelerated reactions; however, it was subsequently demonstrated that the mechanism is in fact T cell–dependent [64].

Published studies support the role of a T cell–mediated mechanism in these reactions, as is the case with other drugs. Activation of T cells is observed in both peripheral blood and in the area of skin testing and is detected by the expression of the cutaneous lymphocyte-associated antigen and other chemokine receptors and integrins that interact with their corresponding ligands [65,66].

Several studies of nonimmediate reactions to ICM have shown skin tests to be positive with the ICM involved [15,60,67,68] and with other ICM with similar chemical structures [15,19].

The involvement of T cells was demonstrated by the presence of perivascular infiltrates of these cells in the dermis of the affected area during the acute phase reaction as well as in the positive skin test area. The lymphocyte proliferation test with the ICM involved in the reaction has also yielded positive results [19,69,70].

Some patients react to ICM upon their first exposure [15,19]. One explanation could be that these patients may have been previously sensitized by structurally related molecules.

Clinical Manifestations

The skin is the most affected organ in both immediate and nonimmediate reactions. Immediate Reactions

The most common symptoms are erythema and urticaria with or without angioedema, which appears in more than 70% of patients [71]. More severe symptoms include dyspnea,
nausea, vomiting, and hypotension. In the most severe cases, anaphylactic shock and acute coronary syndrome (Kounis syndrome) can occur [72].

The severity scales of Ring and Messmer [73] or Brown [74] can be used to classify the reactions.

Nonimmediate Reactions

Most reactions occur in the first 3 days after the administration of ICM. They are usually mild to moderate and generally resolve within 7 days [75,76]. Maculopapular rash is the most common skin manifestation (30-90%), followed by delayed urticaria, with or without angioedema (40%-60%). Contact dermatitis and fixed drug eruption have also been described. More severe manifestations, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized pustulosis, and vasculitis are rare in patients who experience a nonimmediate reaction [12,33].

Nonallergic Reactions

Clinical manifestations such as heat, facial flushing, dizziness, and nausea can occur immediately after administration of ICM and usually resolve spontaneously. Nonallergic reactions are not suggestive of allergic reactions [77]. They usually occur within the first hour after administration, but can happen after longer intervals and be confused with accelerated reactions; however, these reactions are usually milder.

Diagnosis

The evaluation of patients with reactions to ICM can be initiated during the acute phase. In immediate reactions, serial measurements of serum tryptase (at the onset of the reaction and 2 and 24 hours later) can help to identify the type of reaction [59,78]. A 2-fold increase above baseline levels is suggestive of anaphylaxis (grade of recommendation, C) [79].

In nonimmediate reactions, systemic involvement can be evaluated using a complete blood count and serum chemistry, which enable detection of peripheral blood eosinophilia and evaluation of renal and hepatic function (grade of recommendation, D). Performing a biopsy of the affected skin can provide information about the underlying disease process (grade of recommendation, D).

Once the reaction has resolved, the patient should be assessed using available methods for the diagnosis of reactions to ICM, including clinical history, skin tests, in vitro methods, and controlled administration.

Clinical History

The clinical history should be taken carefully, as with any adverse drug reaction. Details should include the ICM administered, the interval between administration of the ICM and the onset of symptoms, the symptoms themselves, and the treatment required to control symptoms. The history should also take account of possible previous administration of ICM and subsequent tolerance to this ICM or others (grade of recommendation, D).

Unfortunately, reactions are not often adequately recorded, thus complicating the subsequent allergy workup.

Skin Tests

Prick and intradermal skin tests should be performed in immediate reactions [80]. The ICM should be used undiluted for skin prick tests and diluted at 1:10 for the intradermal test (grade of recommendation, C) [15]. In the case of severe reactions, intradermal tests should begin with higher dilutions (grade of recommendation, C) [81]. Skin testing should be performed with the ICM involved in the reaction if known. If the result is positive, or if the culprit ICM is unknown, skin testing should be performed with the broadest possible panel of ICM (grade of recommendation, D).

The sensitivity of skin tests for immediate reactions varies from 4.2% to 73% [15,16,77,82]. Such high variability may be due to the different concentrations used in the studies (undiluted ICM can be associated with false positives), the time between the reaction and the study, the clinical symptoms of the patients included, symptom severity, and the type of ICM (ionic or nonionic) [81]. As occurs with IgE-mediated reactions to drugs, if the time between the reaction and the study is longer, the chance of obtaining a positive result will be lower [83,84]. The specificity of intradermal skin tests is estimated at 96.3% [80]. Although the negative predictive value has been shown to be as high as 96.6% [67], it decreases to 60% when controlled exposure tests with ICMs are performed [16].

In nonimmediate reactions, intradermal tests are performed at a 1:10 dilution and patch tests with undiluted ICM. In both cases, the reading should be taken at 48, 72, and 96 hours and occasionally at 7 days (grade of recommendation, C) [15]. Since intradermal testing does not induce false positives in nonimmediate reactions [33], if an intradermal test result is negative at the 1:10 dilution, testing can be repeated with the undiluted ICM (grade of recommendation, C). The intradermal test has higher sensitivity than the patch test [19,33]. The negative predictive value of skin tests for nonimmediate reactions is not well established [35,85]. For both immediate and nonimmediate reactions, skin tests should be performed 2-6 months after the reaction; after this period, the number of positive skin test results will be lower (grade of recommendation, D) [15]. Evidence for this statement is rather limited.

In Vitro Methods

The basophil activation test is used to detect basophil activation markers (CD45, CD18, and CD63) by means of flow cytometry. The basophil activation test is increasingly used with drugs such as β-lactams [86], quinolones [57], protein pump inhibitors [87], corticosteroids [56], and ICM [16]. Data obtained in preliminary studies of patients who experienced immediate reactions to ICM have shown promising results. Activation was detected in 62.5% of patients with hypersensitivity to ICM confirmed by positive skin and/or provocation tests (grade of recommendation, D) [16,82,88]. This technique is not widely available and needs to be validated in various populations.

The lymphocyte transformation test is based on the ability of T cells to proliferate upon contact with ICM in
sensitized patients. Sensitivity was variable in patients who experienced nonimmediate reactions (13-75%) (grade of recommendation, D) [25,33]. This test is not currently used in routine diagnosis. More physiologically relevant tests such as coculture of dendritic cells and lymphocytes may be useful in the future, although further research is required [70].

**Drug Provocation Tests**

The drug provocation test (DPT) is considered the gold standard for the diagnosis of drug hypersensitivity reactions. In many instances, particularly in the case of severe reactions, an alternative ICM can be tried in order to verify tolerance or assess reactivity. Such tests can confirm or exclude the diagnosis when there is no other available evidence and can be used to look for an alternative ICM. The ICM to be administered will be chosen depending on the results of skin and in vitro testing, the ICM that induced the reaction (when known), the severity of the reaction, the availability of alternative ICM, and available information about potential ICM cross-reactivity.

The DPT is performed by administering increasing doses of the ICM (5, 15, 30, and 50 cc) at 30-45–minute intervals [16,81] for immediate reactions and at 1-hour intervals for nonimmediate reactions. In the case of severe nonimmediate reactions, incremental doses must be administered in 2 separate sessions with a gap of at least 1 week between sessions. The dose must be increased gradually: 5, 10, and 15 cc on the first day (cumulative total of 30 cc) and 20, 30, and 50 cc on the second day, a week later (cumulative total of 100 cc) (grade of recommendation, C) [19].

Intravenous administration of ICM can cause acute kidney damage, which is usually reversible. Its incidence is variable, ranging from 0% to 55%, and is higher in the presence of associated risk factors (underlying renal disease with serum creatinine >1.5 mg/dL, diabetic nephropathy, advanced heart failure, or other causes involving reduced renal perfusion [eg, hypovolemia, anemia, percutaneous coronary intervention, and multiple myeloma]). The osmolality and amount of ICM given are also important, with higher-osmolality ICM and doses higher than 140 mL, or repeated doses within 48 hours, more likely to lead to damage. The concomitant use of diuretics, metformin, or nonsteroidal anti-inflammatory drugs is another factor to consider. We suggest that low-osmolality or isosmolar ICMs should be given in patients who experience kidney damage (grade of recommendation, C) [50]. Furthermore, depending on the individual risk, it is recommended to administer oral serum bicarbonate, oral N-acetylcysteine, and intravenous saline solution (0.9%) according to different published regimens before and after ICM as prophylaxis against renal damage [89].

**Cross-reactivity**

Cross-reactivity between ICM is less common in immediate reactions [33] and is related to chemical structure [90]. The association most frequently detected is between iodixanol, iohexol, iopentol, ioversol, and iomeprol. This is particularly relevant between iodixanol and iohexol monomers. Other ICM such as ioxaglate, iopamidol, iobitridol, and iopromide have limited cross-reactivity [15,19] (Table 2).

### Table 2. Cross-reactivity of ICMs

<table>
<thead>
<tr>
<th>Association</th>
<th>Frequent Associations</th>
<th>Limited Associations</th>
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<tr>
<td>Iodixanol</td>
<td>Iodixanol</td>
<td>Ioxaglate</td>
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<tr>
<td>Iohexol</td>
<td>Iohexol</td>
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<td>Iopentol</td>
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<td>Iomeprol</td>
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Given the different patterns of cross-reactivity, skin tests based on as wide a battery of ICM as possible are recommended (grade of recommendation, D) [91]. However, since a negative skin test result to an alternative ICM does not necessarily mean the patient will not respond to its administration, controlled administration is also recommended.

**Algorithm**

The recommended diagnostic algorithm is provided in Figure 2. Nonhypersensitivity reactions do not require an allergy study. Suggestive hypersensitivity reactions can be immediate or nonimmediate.

In the case of immediate reactions, the first approach is to perform skin prick tests with a battery of ICM and take a reading 15-20 minutes after application. If the results are negative, an intradermal test should be performed. In the case of a negative skin test result for the culprit ICM, a DPT should be performed (although not if the patient had previously experienced a severe reaction). If skin testing gives a positive result for the culprit ICM, a DPT should be performed with an alternative ICM that gave a negative skin test result in order to identify a safe alternative.

Nonimmediate reactions to intradermal and patch tests with delayed readings should be performed with a battery of ICM. If the results are positive, alternatives should be sought using the procedure described for immediate reactions. In the case of negative skin test results, the approach will depend on whether the reaction was mild or moderate to severe. In the first case, the DPT will be performed with the culprit ICM on a single day. In the second case, the DPT will be performed with an alternative ICM over 2 days. In patients with severe medical reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, or acute generalized exantheme putulosis, as well as in patients with organ-specific reactions (eg, ICM-induced hepatitis), readministration of the culprit ICM is absolutely contraindicated, even when the result of the skin test is negative. In these situations, the administration of an alternative ICM should only be considered if absolutely necessary, and a careful analysis of the potential risks and benefits should be performed.

**Treatment**

Early recognition of a reaction is essential for proper treatment. This should not prove difficult if the reaction...
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**ADVERSE REACTIONS TO RADIOLOGIC CONTRAST MEDIA**

<table>
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<tr>
<th>SUGGESTIVE HYPERSENSITIVITY REACTION</th>
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<tr>
<td>IMMEDIATE REACTION</td>
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<tr>
<td>SKIN PRICK TEST AND INTRADERMAL TEST</td>
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<td>+</td>
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<tr>
<td>EXPOSURE TEST WITH AN ALTERNATIVE ICM ON 1 DAY</td>
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</tbody>
</table>

| NONIMMEDIATE REACTION                |
| PATCH TEST AND INTRADERMAL TEST      |
| +                                    |
| EXPOSURE TEST WITH THE CULPRIT ICM ON 1 DAY |

| MODERATE-SEVERE REACTION             |
| NO STUDY NEEDED                      |

**NONSUGGESTIVE HYPERSENSITIVITY REACTION**

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is reported in the setting where it occurs, although it is rather uncommon if the reaction occurs 24-48 hours after administration of the ICM. Therefore, following a radiological examination with ICM, the patient should remain under observation for at least 30 minutes (grade of recommendation, C) [92]. It is essential that patients undergoing treatment with ICM be given instructions on how to proceed in a nonimmediate reaction.

First-line drugs for treatment of anaphylaxis must always be available, as should the equipment and trained personnel required for its management, including potential cardiac arrest. If symptoms appear, the ICM infusion should be interrupted immediately, and an appropriate treatment administered [27,93]. Some authors propose that mild reactions such as itching and hives are usually self-limiting and thus do not require treatment [93], although they are usually treated with anti-H1 blockers (grade of recommendation, D) [27]. It is always necessary to maintain venous patency, and the patient should be observed carefully for possible progression to more severe symptoms. Treatment of systemic reactions is administered according to the GALAXIA guide for anaphylaxis [79]. Mild and moderate bronchospasm should be treated with oxygen and inhaled β2-agonists (grade of recommendation, B) [93]. Anaphylactic reactions require treatment with epinephrine (grade of recommendation, A) [93].

The value of premedication is rather controversial and may induce a false sense of security, especially when it is administered systematically without a prior allergy study (grade of recommendation, D). It has only been shown to reduce the occurrence of mild immediate reactions and has not been demonstrated to be useful for immediate moderate to severe and nonimmediate reactions [46,94,95].

Guidelines from ENDA in 2005 recommended the use of premedication when administering an alternative ICM that gave a negative skin test result. However, following the results of several studies that evaluated controlled challenge [16,19,81], the use of premedication is being questioned (grade of recommendation, D) (see diagnostic algorithm, Figure 2).

The most common premedication protocol used is oral prednisone 50 mg or intravenous methylprednisolone 40 mg administered 13, 7, and 1 hour before injection of ICM, with intravenous dexchlorpheniramine 5 mg also given 1 hour before. If an urgent radiological examination with ICM is needed, intravenous hydrocortisone 200 mg and intravenous dexchlorpheniramine 5 mg should be administered 1 hour before injection of ICM (grade of recommendation, D) [71].

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### Reactions to Other Radiologic Contrast Media

The most frequently used noniodinated radiologic contrast media are barium and paramagnetic agents.

#### Barium Contrast Media

Barium contrast agents contain barium sulfate and are used to visualize areas of the digestive tract [96]. They are administered orally or rectally. The most common adverse reactions are mild and nonallergic and include diarrhea, constipation, nausea, and vomiting.
The prevalence of allergic reactions is less than 2 per million [96,97], although this frequency is increasing [98]. Barium sulfate is inert and nonantigenic and is generally not absorbed by the intestinal tract. However, some additives present in barium formulations such as carboxymethylcellulose and methylparaben are absorbed and might be responsible for adverse reactions [99-101]. In addition, drugs such as glucagon, which are used to reduce discomfort during scans with barium sulfate, have also been implicated in allergic reactions [102].

**Contrast Media Used in MRI**

Most paramagnetic contrast media used in MRI are gadolinium chelates or complexes [103,104]. These molecules are classified depending on their net charge as ionic or nonionic and on their structure as linear or macrocyclic (Figure 3).

Immediate hypersensitivity reactions to gadolinium derivatives are the most frequently described, with an incidence of 0.07% in adults and 0.04% in children [103,104]. Reactions have been reported more frequently for abdominal explorations (0.01%) than for explorations of the brain (0.005%) or spine (0.003%) [105] and after administration of dimeglumine gadobenate and gadoteridol [104-107].

The risk factors for reactions to paramagnetic contrast media are very similar to those described for ICM. The main risk is that of recurrence, which affects 30% of patients who have already experienced a reaction. Female gender and a history of rhinitis or asthma, food allergy, and hypersensitivity reactions to other drugs have also been associated with an increased risk of reaction [104].

The symptoms described with gadolinium chelates are very similar to those of immediate reactions to ICM and are mostly mild [104,105]. The most common clinical manifestation is urticaria (50-90% of cases). Anaphylactic reactions are rare, with an incidence of 0.004% to 0.01% [20,104]. To our knowledge, nonimmediate hypersensitivity reactions to gadolinium chelates have not been described to date, although the possibility of such a reaction occurring cannot be ruled out.

The pathophysiological mechanisms underlying these reactions are not well known. Involvement of specific IgE has been suggested, based on positive skin test results in patients with anaphylactic reactions to MRI contrast media [20-23].

Several cases of anaphylaxis with gadolinium chelates (meglumine gadoterate, gadoteridol, and dimeglumine gadopentetate) have been reported [104,105,108]. In some cases, positive results were detected using undiluted contrast for skin prick tests and dilutions of 1:1000 to 1:10 for intradermal tests (grade of recommendation, D) [21-23,109,110]. Cross-reactivity between gadolinium chelates is still unclear [22,23,111], although it appears not to exist between macrocyclic and linear substances. In the case of immediate hypersensitivity reactions, it would be advisable to use gadolinium chelates as an alternative to the culprit, preferably with a different molecular structure (grade of recommendation, D). Skin testing should also be performed (grade of recommendation, D) [23,112].

**Comments and Further Research**

Contrast media are increasingly used worldwide, with millions of explorations being performed every day. Therefore, although these reactions are rare, they occur regularly and are often severe and even life-threatening [16].

The search for alternative ICM is critical, given that many patients require ICM-based procedures for diagnosis and disease monitoring. Therefore, we must distinguish between the different types of reactions where immunological mechanisms are involved (ie, nonallergic and true allergic hypersensitivity reactions) [52]. ICM can cause a wide variety of clinical conditions that are induced by different mechanisms and vary in terms of severity, the diagnostic procedures involved, and the choice of alternatives [113].

The efforts made by the ENDA and EAACI groups are key to progress in this area and will lead to major clinical benefits [18,114].

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**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

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5. Summary of key points:
   - Immediate and delayed reactions to radiocontrast media.
   - Role of allergy in contrast media reactions.
   - Management strategies for contrast media-induced anaphylaxis.

6. Keywords: contrast media, hypersensitivity, anaphylaxis, management.
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II Ana Rosado Ingelmo

Unidad de Alergia
Hospital Universitario Fundación Alcorcón
c/ Budapest, 1
28922 Alcorcón, Madrid, Spain
E-mail: arosado@halcorcon.es


