European Journal of Radiology 190 (2025) 112194

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Review

Allergological evaluation of hypersensitivity reactions after administration of contrast agents: What the radiologist needs to know

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ARTICLE INFO

Keywords:
Contrast media
Cross-reactivity
Drug provocation test
In vitro test
In vivo test
Skin tests

ABSTRACT

Objective: To familiarize radiologists with the methodology used in the assessment and management of hypersensitivity reactions to contrast agents.
Methods: This review provides diagnostic tools for the appropriate identification this type of reactions, including a checklist of key clinical items and a proposed algorithm to differentiate hypersensitivity reactions from nonspecific reactions and to assess their severity. It also outlines the main *in vitro* techniques (specific IgE, basophil activation test, mast cell activation test, lymphoblastic transformation test, and ELISpot) and *in vivo* procedures (skin tests and drug provocation tests) used to identify the culprit contrast agent and guide the selection of a safe alternative.
Results: Although premedication is commonly used, its effectiveness is limited. Administering an alternative contras agent is a more effective strategy, but empirical selection carries a risk of recurrence. Allergy testing enables safer selection of an alternative agent. Integrating allergy evaluation into radiological practice can improve patient safety and outcomes in patients with a history of previous reactions.
Conclusion: Allergological techniques are valuable tools that support radiologists in the safe management of patients with hypersensitivity reaction to contrast agent, particularly in cases requiring re-exposure. The article concludes by presenting a diagnostic algorithm for both immediate and delayed reactions.
Clinical relevance statement: Switching to an alternative contrast agent is the most effective way to prevent a new hypersensitivity reaction. Radiologists should be familiar with the *in vivo* and in vitro techniques used in the allergy work-up to select a safe alternative agent.

Abbreviations: ACR, American College of Radiology; AGEP, Acute generalised exanthema pustulosis; BAT, Basophil activation test/tests; CA, Contrast agent/agents; CD, Cluster of differentiation; CFSE, Carboxyfluorescein diacetate succinimidyl ester; CR, Cross-reactivity; DPT, Drug provocation test/tests; DRESS, Drug reaction with eosinophilia and systemic symptoms; EAACI, European Academy of Allergy and Clinical Immunology; ESCD, European Society of Contact Dermatitis; ESUR, European Society of Urogenital Radiology; GBCA, Gadolinium-based contrast agent/agents; GBFDE, Generalized bullous fixed drug eruption; HR, Hypersensitivity reaction/reactions; ICM, Iodine-based contrast medium/media; IDT, Intradermal test/tests; IgE, Immunoglobulin E; IHR, Immediate hypersensitivity reaction/reactions; LTT, Lymphocyte transformation test/tests; MAT, Mast-cell activation test/tests; MRGPRX2, Mas-related G-protein coupled receptor member X2; NIHR, Nonimmediate hypersensitivity reaction/reactions; PT, Patch test/tests; SCAR, Severe cutaneous adverse reaction/reactions; SJS/TEN, Stevens Johnson syndrome/toxic epidermal necrosis; SPT, Skin prick test/tests; ST, Skin test/tests; USCA, Ultrasound contrast agent/agents.

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https://doi.org/10.1016/j.ejrad.2025.112194
Received 17 May 2025; Accepted 21 May 2025
Available online 24 May 2025

1. Introduction

Contrast agents (CA) are drugs used in diagnostic and therapeutic radiological procedures. Diverse types of CA are used to perform various radiological techniques. Although in some situations a same CA may be used across multiple techniques, they are generally associated with a specific type of imaging: iodine-based contrast media (ICM) for X-ray examinations, gadolinium-based contrast agents (GBCA) for magnetic resonance imaging, and microbubble ultrasound contrast agents (USCA) for ultrasound (Table 1). They can cause adverse chemotoxic reactions (Type A reactions) as well as hypersensitivity reactions (HR) (Type B reactions).

HR can occur even with small amounts of CA, and a prior reaction to a CA remains the strongest risk factor for experiencing a subsequent HR [1,2]. It is crucial to distinguish a true HR from a Type A reaction, either chemotoxic/osmotoxic or non-specific in nature. These are named *physiological reactions* by the ACR (American College of Radiology), and some can be triggered by anxiety or a vagal response. HR are classified as immediate HR (IHR) when they occur within the first hour after CA administration, and delayed HR (NIHR) if they develop between 1 h and 1 week after administration. However, in cases of severe NIHR, onset may be further delayed. Although most reactions are mild [3], there is a potential risk of life-threatening manifestations such as anaphylaxis in IHR [4], or severe cutaneous adverse reactions (SCAR) in NIHR [5]. Fig. 1 presents an algorithm designed to identify the HR and to assess their severity.

When a true HR is suspected, treatment should be initiated according to the severity of symptoms and the patient's comorbidities. All information related to the event should be documented in the patient's medical record, with particular emphasis on identifying the implicated CA. Whenever possible, all HR, regardless of severity, should be referred for allergy evaluation, which is mandatory in the case of severe reactions. Table 2 provides a checklist outlining the key aspects to consider in the management of an HR.

The aim of this review is to familiarize radiologists with the methodology used in CA allergy evaluations and to highlight the contributions of allergologists in optimizing the management of these patients. All the tests discussed below can be applied to investigate HR to any type of CA, including ICM, GBCA, and microbubble agents.

Table 1
Classification of contrast agents according to their use in Radiology and the chemical characteristics of their molecules.

Iodine-based Contrast Media (ICM) for X-Ray Examinations	
Ionic ICM	Diatrizoate meglumine/sodium
	Ioxithalamate meglumine/sodium
Non-Ionic ICM	Iohexol
	Ioversol
	Iomeprol
	Iodixanol
	Iobitridol
	Iopromide
	Iopamidol
Gadolinium-Based Contrast Agents (GBCA) for Magnetic Resonance Imaging	
Linear GBCA	Gadopentetate dimeglumine
	Gadobenate dimeglumine
	Gadoxetate disodium
	Gadodiamide
Macrocyclic GBCA	Gadoterate meglumine
	Gadoteridol
	Gadobutrol
	Gadopiclenol
Microbubble Ultrasound Contrast Agents (USCA) for Ultrasound	
Microbubbles	Phospholipid-encapsulated microbubbles containing perfluoropropane
	Albumin-coated microbubbles containing perfluoropropane
	Hydrogenated egg phosphatidyl serine-encapsulated microbubbles containing perfluorobutane
	Phospholipid-encapsulated microbubbles containing sulphur hexafluoride

2. Management of a patient with a previous reaction to contrast agent

There are no standardized protocols or recommendations for preventing recurrent HR to CA, and over the years, different strategies with varying degrees of success have been proposed. The most used recommendations are summarized below:

- **Avoid re-exposure to CA** by performing unenhanced radiological studies [6]. Unfortunately, the use of contrast-enhanced imaging is considered essential for accurate evaluation in many cases. Then, a failure to perform such studies appropriately could compromise the quality of patient care.
- **Perform enhanced imaging with a different type of CA.** ICM and GBCA, especially ionic ones, do not exhibit cross-reactivity (CR) and can therefore be used as alternatives [7]. This option may not always be feasible, for example in angiographic studies, and may be less effective and/or more expensive. It should be noted that there is a possibility of CR in the case of ionic CA containing meglumine, as meglumine has been shown to activate mast cells through non-immunoglobulin-mediated mechanisms [8]. It should also be considered that HR might occur with various CA due to sensitization to trometamol, a preservative present in multiple CA, including both ICM and GBCA [9].
- **Reduce the dose or dilute the CA, and/or decrease the injection rate.** This strategy could reduce the occurrence of non-immunoglobulin-mediated IHR, which may require high concentrations of CA to be triggered, but it would not prevent IgE/IgG-mediated IHR or NIHR driven by T-cell responses, which are dose-independent. Moreover, reducing the injection rate or dose may compromise the quality of radiological imaging and is particularly difficult to apply in vascular imaging techniques, which require high-flow CA administration.
- **Premedication with corticosteroids and antihistamines** prior to CA administration has long been the most commonly used prevention. However, its effectiveness is now being questioned [10–12]. Breakthrough reactions can occur despite premedication [13,14], with an incidence ranging from 1.2 % to 46 % [15–17]. As a result, premedication is no longer recommended in several international guidelines, such as the European Society of Urogenital Radiology (ESUR) [18], the European Academy of Allergy and Clinical Immunology (EAACI) [19], and more recently, the Canadian consensus developed by allergologists and radiologists [20].
- **Use of an alternative contrast agent.** Growing evidence supports the greater safety of recommending alternative CA [21,22]. However, empirical switching to a different CA formulation can be challenging due to the high and variable CR among them [19]. While some recent studies have evaluated this CR [23–26], some authors have attempted to classify ICM and GBCA into homogeneous groups based on molecular similarity to facilitate empirical selection [27,28]. An appealing approach to guide empirical switching is to compile data from previous studies on HR to CA. In this regard, we present two summary tables (Table 3 addressing IHR and Table 4 focusing on NIHR) based on cumulative data on cross-reactivity between ICM from large ST studies [26,29,30]. However, these proposals currently lack sufficient clinical validation; therefore, empirical selection may be considered in emergencies or in cases of mild or moderate hypersensitivity reactions (HR), but its use is more difficult to justify in severe cases, such as anaphylaxis or SCAR.

Whenever possible, the best outcomes in selecting an alternative CA are achieved when the choice is guided by prior allergy evaluation

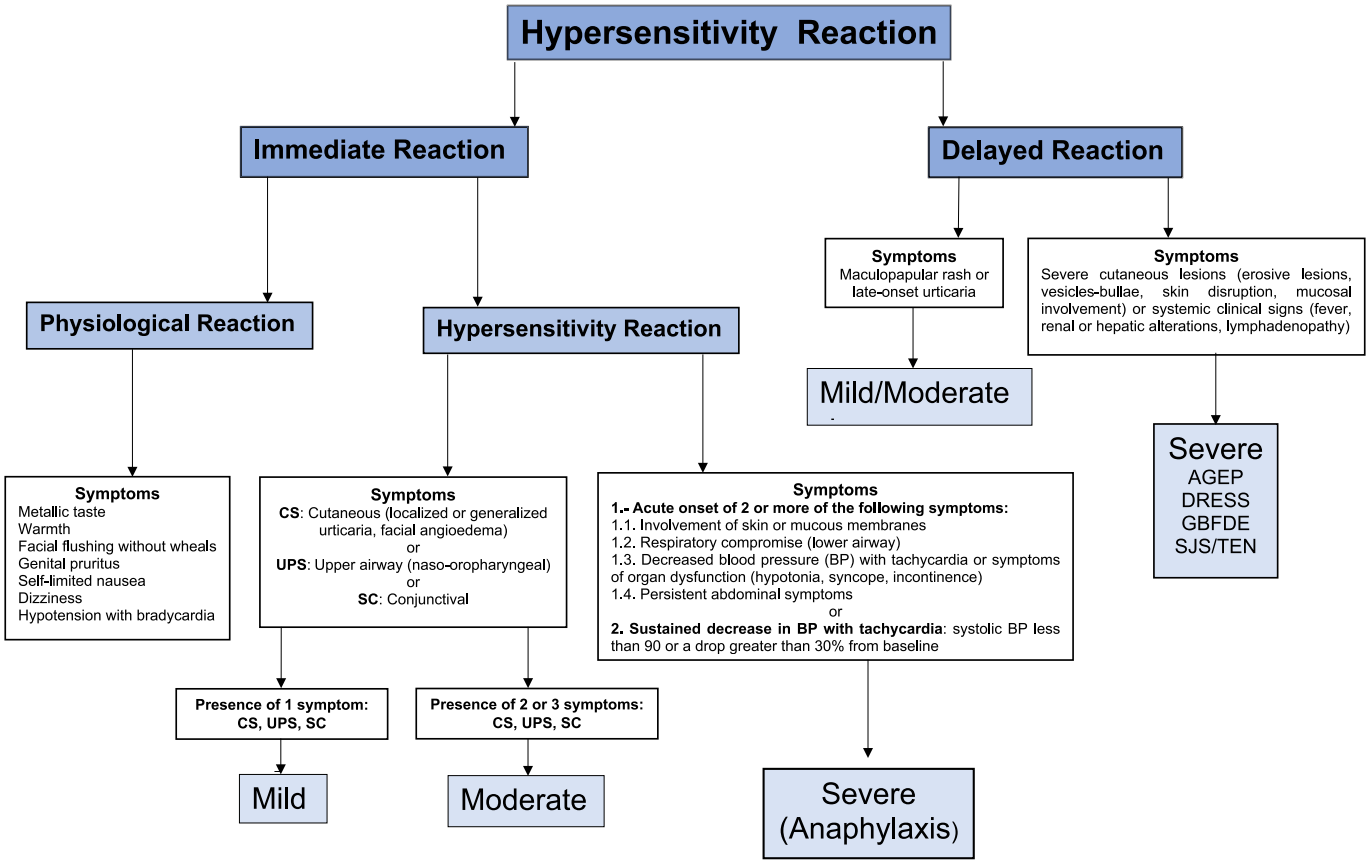

Fig. 1. Differential diagnosis of hypersensitivity reactions to contrast agents and assessment of their severity. AGEP: Acute Generalized Exanthematous Pustulosis; DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms; GBFDE: Generalized Bullous Fixed Drug Eruption; SJS/TEN: Stevens-Johnson Syndrome /Toxic Epidermal Necrolysis.

[19,30,31]. To implement this, it is crucial to obtain a thorough clinical history documenting the characteristics of the reaction and the implicated CA. Then, radiologists should routinely include this information in the imaging report to aid in subsequent evaluations.

The patient should be referred for evaluation by an allergologist as soon as possible after the reaction occurs, although the allergy study should ideally be performed within two to six months after the initial reaction [31,32]. Conducting the study too soon may be less effective, as the patient might be in a refractory phase [33,34]. On the other hand, delays beyond this period reduce the study's efficacy due to the loss of sensitization over time [31,35]. Moreover, in many cases, key information such as the description of symptoms, severity, and identification of the implicated CA is not recorded in the patient's medical history. In such cases, a longer delay is associated with a higher risk of recall bias [36].

The following section provides a detailed description of *in vivo* and *in vitro* tests used to perform an allergy evaluation for CA-related HR. *In vivo* tests, especially ST, are the most commonly used tools in clinical practice for the allergy assessment of HR to CA. In contrast, *in vitro* tests are more limited in availability, as many centres do not have access to these techniques. For this reason, they are often used in research settings; however, their use in clinical practice is advisable in the evaluation of severe HR, prior to conducting *in vivo* tests, which carry a higher risk for the patient.

3. *In vitro* assessment of hypersensitivity reactions to contrast agents

In vitro methods aim to complement clinical history, skin testing, and provocation tests, especially in cases where these methods are contraindicated or entail significant risks. These laboratory methods are used in routine practice in drug allergy studies, although their suboptimal sensitivity and, especially, their restricted availability limit their use. Standardization of testing protocols and further validation in diverse patient populations are necessary to improve the reliability of these tests [37,38]. *In vitro* strategies differ between the evaluation of IHR and NIHR.

3.1. *In vitro methods to study immediate hypersensitivity reactions*

3.1.1. *Quantification of mast cell mediators*

Tryptase is a mast cell protease released upon mast cell stimulation, with serum levels remaining elevated for several hours. Measurement of serum tryptase is currently considered the most reliable biomarker for suspecting an IHR [19]. For accurate quantification, two blood samples should be collected from the patient in the acute phase reaction. The first sample should be taken as soon as possible at the onset of the reaction, and the second within 2 h after the first. These levels should be compared with the baseline level, measured at least 24 h post-reaction. An acute elevation of tryptase levels greater than 20 % above baseline plus 2 ng/mL [1.2 × baseline tryptase level + 2 (ng/ml)] is indicative of an IHR with mast cell degranulation [39,40]. Tryptase levels often correlate with IgE-mediated reactions and symptom severity [41,42]. However, the absence of elevation does not exclude the possibility of a genuine IHR reaction [43]. Tryptase measurement is strongly recommended in cases of severe IHR, whereas its utility is limited in mild or moderate cases, and it has no diagnostic value in NIHR.

Histamine is another mast cell mediator involved in IHR. However, it is less commonly used for diagnosis due to its rapid degradation and the complexity of available assays, which limits its utility in clinical settings

Table 2
Checklist for the appropriate management of a hypersensitivity reaction to contrast agent.

	Date	**Time**
Date and Time of Hypersensitivity reaction		
	BP	**HR**
Blood Pressure and Heart Rate		
Cutaneous Symptoms	Yes	No
Oropharyngeal Symptoms	Yes	No
Conjunctival Symptoms	Yes	No
Lower Respiratory Tract Symptoms	Yes	No
Gastrointestinal Symptoms	Yes	No
Cardiac Symptoms	Yes	No
Neurologic Symptoms	Yes	No
Severity	☐ **Mild** ☐ **Moderate** ☐ **Severe**	
Underlying diseases that may worsen symptoms		
Uncontrolled COPD/Asthma	Yes	No
Uncontrolled chronic urticaria	Yes	No
Idiopathic Anaphylaxis	Yes	No
Mastocytosis	Yes	No
Ischemic Heart Disease	Yes	No
Beta-Blocker Use	Yes	No
Treatment administered		
Intramuscular Adrenaline	Yes	No
Antihistamines	Yes	No
Corticosteroids	Yes	No
Intravenous Fluids	Yes	No
Oxygen Therapy	Yes	No
Information about the Contrast Agent		
Name of Contrast Agent Administered		
Dose		
Time Until Symptom Onset		
Previous Hypersensitivity Reactions to CA	Yes	No
Culprit CA in previous Hypersensitivity Reaction		
Referral for Allergy Evaluation	Yes	No

[19,27,31]. Thus, serum tryptase is generally preferred for diagnosing IHR [27,37,38].

The determination of these mast cell mediators confirms the occurrence of an IHR but does not identify the causative antigen. Therefore, it does not allow confirmation of the involvement of a CA in the reaction. Consequently, additional methods, described below, can be performed to establish this implication.

3.1.2. Determination of specific IgE antibodies

Specific IgE detection in serum is traditionally performed using a solid-phase immunoassay, especially in the diagnosis of inhalant and food allergies. However, only a limited number of drug-specific IgE assays are currently available [44–46]. The feasibility of this test is hindered by the nature of drugs as antigens, as they are small molecules that often require a carrier to become reactive. Additionally, in some cases, the actual antigen could be a drug metabolite.

This test has high specificity but limited sensitivity, and its results do not correlate with symptom severity. Furthermore, proper validation would be necessary before incorporating it into routine clinical practice for drug hypersensitivity evaluation [47,48]. These methodological challenges explain why only a few studies have reported the detection of IgE recognizing a CA [49,50], and currently, this technique is limited to research use.

3.1.3. Basophil activation test

The Basophil Activation Test (BAT) is a flow cytometry-based assay that detects activation of cell membrane cluster of differentiation (CD) markers such as CD63, CD18, and CD45 on basophils after allergen stimulation. BAT has shown acceptable sensitivity (46 %-63 %) and excellent specificity (89 %-100 %) for diagnosing IHR to ICM [27,37,51], and even slightly higher results with GBCA, with a specificity of 93 % and a sensitivity of 69 % [21]. Similar to the determination of specific IgE, the results do not correlate with symptom severity [47].

This technique evaluates basophil activation in IgE-mediated reactions, but also in other alternative mechanisms. Since basophils, unlike cutaneous mast cells, express only low levels of Mas-related G-protein-coupled receptor member X2 (MRGPRX2) on their surface, they may not respond under steady-state conditions in conventional BAT. Therefore, unlike IgE-mediated reactions, IHR driven by MRGPRX2 activation may yield negative BAT results [52].

Additionally, it should be considered that in about 10 % to 20 % of patients, basophils cannot be activated by positive control stimuli or specific drugs and are referred to as non-responders [44]. To overcome these technical limitations, techniques using mast cells instead of basophils have been developed.

3.1.4. Mast-cell activation test

The essential role of mast cells in IHR implies that any in vitro technique based on the quantification of their activation undoubtedly improves the sensitivity of the laboratory test. In this context, the Mast-cell Activation Test (MAT) is a flow cytometry-based assay that allows for the detection of mast cell activation. Given that mast cells express a higher number of IgE-independent receptors than basophils, such as MRGPRX2, MAT may offer greater sensitivity than BAT for identifying non–immunoglobulin-mediated HR [53–55]. Mast cell precursors from allergic patients could be employed [56,57], but their uses present several challenges, such as the requirement for a large volume (approximately 100 mL) of fresh blood from the patient. For this reason, mast cell lines derived from donor progenitor cells, such as LAD2 or LADR cells [58,59], are commonly used. These cells can be useful for studying HR mediated by the binding of IgE/IgG to their receptors, but they are not suitable for assessing reactions involving other mast cell receptors. Thus, MAT emerges as a promising technique in the study of IHR, both with ICM [50,60,61] and GBCA [8].

3.2. In vitro methods to study nonimmediate hypersensitivity reactions

3.2.1. Lymphocyte transformation test

The Lymphocyte Transformation Test (LTT) is a cellular-based test used to reveal the presence of drug-specific memory T-cells in circulating blood and assess their proliferative response to identify the culprit drug. These drug-specific T-lymphocyte responses are measured by the incorporation of ^{3}H-thymidine or the use of the stable dye CFSE (carboxyfluorescein diacetate succinimidyl ester) during lymphocyte proliferation. Its variable sensitivity and technical complexity limit its widespread use in routine clinical practice. LTT has been used to demonstrate the specific recognition of CM by T-lymphocytes in patients with NIHR [62,63]. It shows high specificity, although false-positive results may occur with CA [64], but its sensitivity ranges from 13 % to 75 % [65], being lower in more severe reactions [44]. The negative predictive value of LTT has not been established; therefore, a negative LTT result cannot exclude the involvement of ICM. The test is not recommended during the acute phase but rather between 4–8 weeks after remission [66] and within 2–3 years of the reaction [64].

Table 3
Cross-reactivity rates between pairs of iodine-based contrast media (ICM) in skin-positive patients with immediate hypersensitivity reactions to ICM.

ICM Name	Iobitridol	Iopamidol	Iopromide	Iohexol	Iomeprol	Ioversol	Iodixanol
Iobitridol	X						
Iopamidol	**12.7%** [5.9-22.1]	X					
Iopromide	**10%** [5.9-12.1]	**14.3%** [11.7-19.1]	X				
Iohexol	**9.8%** [5.9-16.4]	**11%** [8.0-14.0]	**12.8%** [5.9-23.6]	X			
Iomeprol	**10.8%** [5.9-16.6]	**10%** [6.0-14.0]	**27.9%** [21-41.1]	**22.2%** [1-36.3]	X		
Ioversol	**8.4%** [6-10.8)	**8%** [5-10.9]	**12.2%** [4-20.4]	**15.3%** [7-23.5]	**19.7%** [8-29.4]	X	
Iodixanol	**9.9%** [7-12.8]	**6.3%** [5-7.6]	**12.4%** [9-16.6]	**16%** [10-20.4]	**15.5%** [11-17.8]	**14.3%** [5-20.4]	X

Average percentages [range] findings by Yoon et al, [26] and Schrijvers et al. [29].
Risk of cross-reactivity is marked as very low (cream < 10 %), low (yellow, 10–20 %), medium (orange 20–30 %), high (red, 30–50 %) and very high (dark red, >50 %).

3.2.2. *Elispot (Enzyme-Linked ImmunoSpot Assay)*

ELISpot (Enzyme-Linked ImmunoSpot Assay), and its evolution FluoroSpot, which involves the use of fluorochrome-conjugated antibodies, have also been employed for the study of NIHR to drugs. Both techniques are designed for cytokine quantification, enabling the identification of immune cell populations through the measurement of their secretory products. However, despite their use in studying NIHR to various drugs, particularly antibiotics and anticonvulsants, their application in the assessment of HR to CA has not yet been reported.

4. *In vivo* assessment of hypersensitivity reactions to contrast agents

The allergic evaluation of HR to CA, both IHR and NIHR, involves *in vivo* techniques, including skin tests (ST), which are the most used, and drug provocation tests (DPT), which are increasingly being employed.

4.1. *Skin tests*

ST are a useful and safe tool with a low rate of systemic reactions [32]. They are recommended as the initial step both for assessing the

Table 4
Cross-reactivity rates between pairs of iodine-based contrast media (ICM) in skin-positive patients with nonimmediate hypersensitivity reactions to ICM.

ICM Name	Iobitridol	Iopamidol	Iopromide	Iohexol	Iomeprol	Ioversol	Iodixanol
Iobitridol	X						
Iopamidol	**11.8%** [5.5-18]	X					
Iopromide	**22.1%** [22-22.2]	**25.6%** [11.1-40]	X				
Iohexol	**20.8%** [16.6-25]	**25.1%** [11.1-39]	**43.5%** [38.9-48]	X			
Iomeprol	**17.6%** [13-22.2]	**33.2%** [33-33.3]	**38.7%** [33-44.4]	**40.2%** [36-44.4]	X		
Ioversol	**20.6%** [19-22.2]	**35.6%** [22.2-49]	**37.7%** [33.3-42]	**50.0%** [38.9-61]	**53.3%** [51-55.5]	X	
Iodixanol	**19.3%** [16.6-22]	**36.6%** [22.2-51]	**45.5%** [38.9-52]	**51.7%** [44.4-59]	**45.5%** [41-50]	**51.5%** [38.9-64]	X

Average percentages [range] findings by Yoon et al. [26] Schrijvers et al. [29], and Sohn et al. [30].
Risk of cross-reactivity is marked as very low (cream < 10 %), low (yellow, 10–20 %), medium (orange 20–30 %), high (red, 30–50 %) and very high (dark red, >50 %).

involvement of a CA in HR [26,67,68] and for guiding the evaluation of tolerability to alternative CA [19,30,35,69,70]. However, in cases of severe HR, and to increase patient safety, in vitro tests should be performed prior to ST whenever possible. ST should be performed using the broadest possible panel of CA [31,71–73], including the CA implicated in the reaction, if known [30,31].

Three types of ST can be used in the allergic workup of a HR to drugs [74]. In the skin prick test (SPT) and the intradermal test (IDT), a small amount of the culprit CA is applied to the volar surface of the forearm, following the technique recommended by the European Academy of Allergy and Clinical Immunology (EAACI) [75]. IDT has greater sensitivity than SPT in the evaluation of IHR [75–77]. For the assessment of NIHR, in addition to the delayed reading of IDT, a third type of ST can be used: the epicutaneous test, also known as the patch test (PT). In Fig. 2, the main ST are shown along with how a positive result is visualized.

SPT is a non-invasive technique in which a drop of CA is applied to the skin, at least 2–3 cm from the wrist and antecubital fossae [78,79]. A slight superficial puncture is then made with a sterile lancet, allowing the allergen to contact epidermal cells. The SPT result is considered positive if a wheal at least 3 mm larger than the negative saline control is observed at 20 min. If the SPT is negative, an IDT is performed. In IDT, a small amount of diluted CA is injected into the dermis using a very fine needle, creating a small elevation (a visible wheal) [80]. The IDT result is considered positive if there is an increase of at least 3 mm in the initial wheal, accompanied by surrounding erythema, also with a reading at 20 min. SPT is performed using undiluted CA and IDT using a 1:10 dilution [19,31,35,72]. In cases of severe reactions, IDT may begin with higher dilutions, such as 1:1000 or 1:100 [31,81]. IDR using undiluted ICM can be used when prior ST results are inconclusive and may be especially useful in the evaluation of NIHR [40,82,83]. Saline is used as the negative control, while histamine hydrochloride serves as the positive control.

Mild and moderate NIHR often present as maculopapular exanthemas, which usually resolve spontaneously or with treatment using antihistamines or oral corticosteroids. However, NIHR can also be severe and fall under the category of SCAR [5]. For the evaluation of NIHR, delayed readings of IDT appear to be the most useful technique, assessing the presence of an erythematous induration at the IDT site 24–48 h after testing [19,72,84]. PT can also be used, and they should be performed according to the recommendations of the European Society of Contact Dermatitis (ESCD) [85,86]. In general, PT should be performed on the upper back using appropriate device chambers with undiluted CA in a vaseline vehicle and left in place for approximately 48 h without removal. Additionally, patients are advised to avoid exercise or showering to prevent dissolving or removing the contrast agent. PT should include two readings: one at the time of removal after 48 h and a delayed reading 96 h later [86,87]. If the results are negative, a follow-up reading may be done later [31,72]. Since delayed readings of PT may become positive after the supervised reading period has ended, patients should be instructed to either return to the allergy department or send a photo of the result.

In SCAR, skin testing is performed only in highly specialized centres and additional safety measures should be implemented. SPT, and particularly IDT, have a limited role due to the significant risk that cutaneous administration of the suspected CA could induce a new episode of SCAR. If they are ultimately performed, testing should be initiated with higher dilutions. They may be used in non-severe cases of acute generalised exanthema pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS) but are contraindicated in generalized bullous fixed drug eruption (GBFDE) and Stevens Johnson syndrome/toxic epidermal necrosis (SJS/TEN) [4,5]. In these severe forms of NIHR, PT is considered a safer alternative due to its lower risk of inducing new episodes.

Regarding the usefulness of ST, most of the data presented below are derived from studies on HR to ICM. Less information is available on GBCA, but their utility is generally considered suboptimal, although negative predictive values (NPV) greater than 80 % have been reported [88]. No significant data are available regarding USCA.

The specificity of ST is greater than 90 %, both for SPT and IDT [1,19,72]. Unfortunately, the positive predictive value remains unknown [47], because performing DPT with a suspected culprit drug in cases of positive ST results raises obvious ethical concerns [1,89]; therefore, administering a CA with a positive ST result should be avoided [30].

The sensitivity of ST in HR ranges from 4.2 % to 73 % across different studies [26,37,90,91], with higher sensitivity observed when the HR is more severe [67]. When the implicated ICM is identified and included in the study, the sensitivity of the ST exceeds 70 % [77]. However, it drops to below 30 % if the ICM is unknown [36].

The NPV has been reported to be higher than 90 % in IHR [19,36,91], but it decreases to 60 %–65 % in NIHR [63]. This high variability may be attributed to several factors: the different concentrations used in the studies (undiluted ICM may be associated with false positives), the time elapsed between the reaction and the study, the clinical symptoms of the patients included, the severity of symptoms, and the type of ICM (ionic or non-ionic) [31,80].

Regarding PT, both the sensitivity and specificity in NIHR are lower than those of IDT [76,77,92]. This lower effectiveness, combined with the fact that these tests are more labour-intensive, means they are not routinely performed in many Allergy Units, except in case of SCAR [5,19].

When ST yields a positive result for a CA, this CA should be contraindicated for future use. However, a DPT with a negative skin-tested CA could be conducted to rule out the involvement of a CM in a previous HR, and to safely recommend an alternative CA [30,31], because a significant percentage of administrations of negative skin-tested CA in real-life settings may still result in a HR [92,93]. In the case of mild NIHR with negative ST or in vitro tests, or when an allergologist is not available, administration of an alternative CA may be considered if needed for a subsequent radiological procedure, without prior tolerance testing with a direct DPT. Informed consent must be obtained, and trained personnel should be available in the radiology setting to manage such reactions.

4.2. *Drug provocation tests*

DPT consists of the controlled administration of a drug to confirm or exclude whether the drug is responsible for an HR. It is considered by many the gold standard for the study of drug allergy and is the final step of the diagnostic algorithm due to the potential risk to the patient [94,95]. The EAACI/ENDA recommends that DPT be performed under medical supervision in a setting equipped to manage severe reactions, including resuscitation equipment, and with personnel trained in recognizing and treating HR [96]. Placebo-controlled DPT is recommended for patients with non-specific or subjective symptoms.

In recent years, the DPT has been incorporated into the study of HR to CA [19], presenting itself as a safe procedure with risks comparable to those of other drugs when performed in experienced centres [4,38,67,90,97]. Despite these recommendations, a major difficulty in the widespread use of DPT with CA is that it is a technique that is not standardized [47,98].

The performance of a DPT should adhere to a series of recommendations when considering the indications and contraindications for the test [96] (Table 5).

The CA to be administered in the DPT should be chosen based on the following variables:

- The data obtained from the clinical history (type and severity of the reaction presented)
- The CA involved (if known), the availability of an alternative CA, and the CR between them [35].

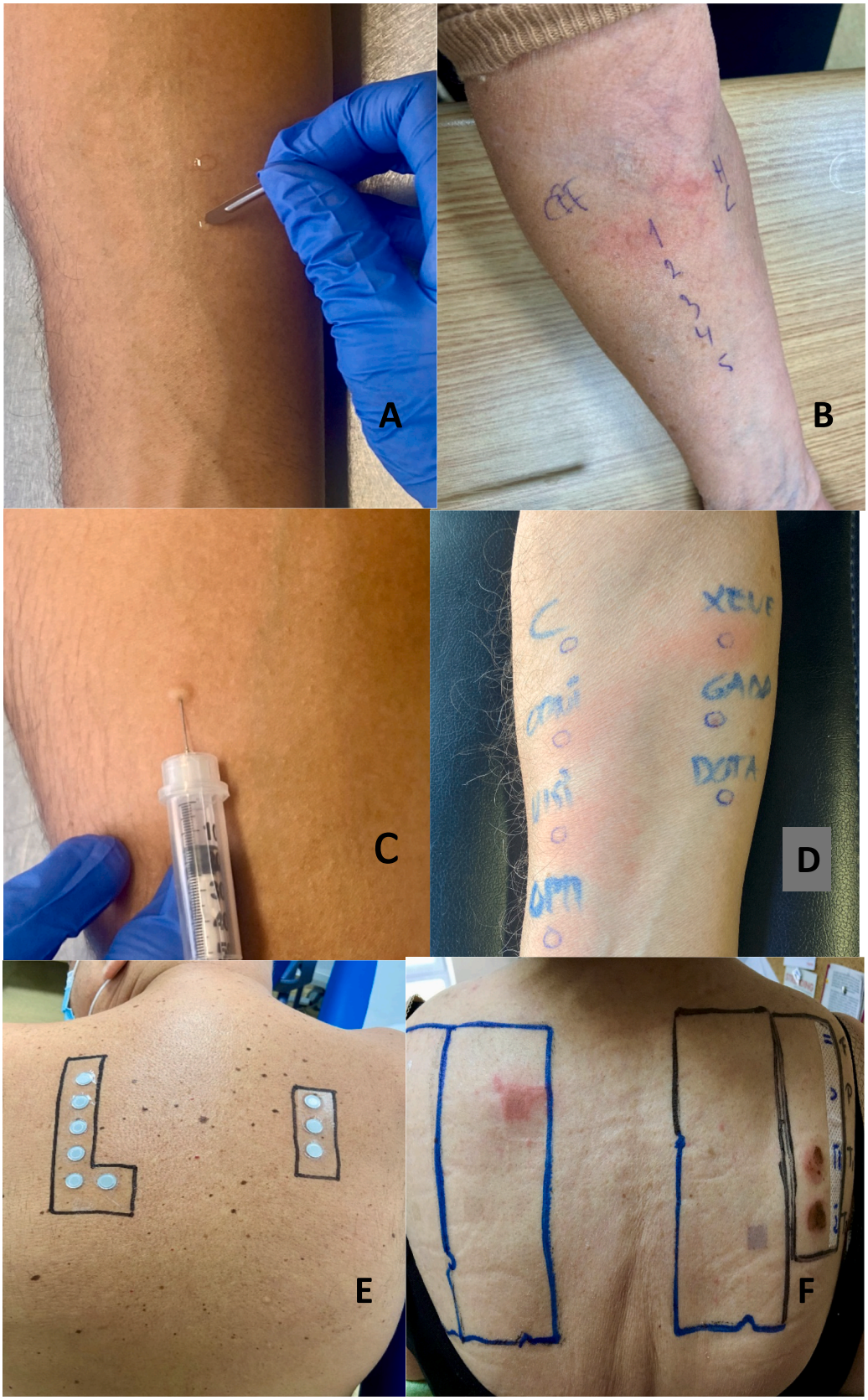

Fig. 2. Skin Testing Technique and Positive Results. A: Skin Prick Test (SPT); B: Positive Result of SPT; C: Intradermal Test (IDR); D: Positive Result of IDR; E: Patch Test (PT); F: Positive Result of PT.

Table 5
Indications and Contraindications for Drug Provocation Tests with Contrast Agents. Modification of Barbaud A, et al. [96].

Indications for Drug Provocation Tests (DPT) with Contrast Agents (CA)
1. **To exclude hypersensitivity** to the suspected CA when the clinical history is nonspecific
2. **To assess cross-reactivity** and identify a safe alternative CA in cases the hypersensitivity reaction (HR) where the culprit CA has been confirmed. A potentially safe alternative CA should be selected based on negative skin tests (ST) prior to DPT
3. **To establish an accurate diagnosis** and demonstrate the involvement of the CA in cases with a history suggestive of a low to intermediate severity HR, but where ST and/or in vitro tests are inconclusive or unavailable
Contraindications to DPT with CA
Absolute Contraindications
1. Severe immediate HR (anaphylaxis) or delayed severe cutaneous adverse reactions (SCAR) to the suspected drug CM. In such cases, DPT with alternative CA may be considered to confirm their tolerance *SCAR include acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), generalized bullous fixed drug eruption (GBFDE), Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).*
2. CA-induced vasculitis, CA-induced specific organ dysfunction (such as cytopenia, hepatitis, nephritis, or pneumonitis), or CA-induced autoimmune diseases (e.g., systemic lupus erythematosus, linear IgA bullous dermatosis
Relative Contraindications
1. Severe comorbidities, including:
• Uncontrolled asthma
• Severe chronic obstructive pulmonary disease (COPD)
• Severe ischemic heart disease
2. Pregnancy, unless the potential benefit clearly outweighs the risk

- Results of skin testing or *in vitro* assays: given the high specificity of these methods, only CA with negative test results should be used [35,67].

The dose of CA administered in the DPT should be close to that used in real-life situations, although in previous studies with ICM, the doses have been highly variable, ranging from 5 ml to 100 ml [28,34,37,95,99]. The use of these very low or diluted doses of ICM has been justified to reduce the risk of causing renal damage, but this risk could be avoided by implementing complementary nephroprotective measures, primarily based on maintaining adequate hydration, if necessary, with intravascular volume expanders [72,100].

Regarding the dosing rate of CA in DPT, the most common method is the application of increasing doses with observation intervals of 30 to 45 min. Therefore, the total time of CA administration is usually 1 to 3 h [37,67,90,101,102]. This slow administration contrasts with the way CA is administered in real life. Most ICM injections in CT employ a power-injector using injection times of 25–40 s (e.g., 100 ml at 3 ml/sec), while GBCA injections in MRI have injection times of 5–10 s. This difference in administration speed may explain the results reported by Meucci et al. [103] and Ahn et al. [104], who found that 7–10 % of patients who used an alternative ICM, with tolerance confirmed through a DPT with slow administration (120 min), experienced a HR when the ICM was administered at high speed during a conventional radiological

Table 6
Protocols for drug provocation tests with iodine-based contrast media (ICM) reported in previous studies.

Drug Provocation Test Protocols with iodine-based Contrast Media							
Type of HR	**Fist Author and year *(reference)***	**Number of patients challenged**	**Progressive Dose**	**Interval between doses**	**Total Dose**	**Total DPT Duration**	**Number of DPT days**
IHR	Trcka 2008 *(37)*	2	0.05–0.5–1-5–7.5–10-25 ml	30 min	49.05 ml	120 min	1
	Salas 2013 *(89)*	8	5–15-30–50 ml	45 min	100 ml	180 min	1
	Sese 2016 *(34)*	37	10 ml	Single dose	10 ml	Not notified	1
	Morales-Cabeza 2017 *(99)*	12	5–30-60 ml (first day) 120 ml (second day)	30 min	95 ml (first day) 120 ml (second day)	60 min	2
NIHR	Vernassiere 2004 *(91)*	5	1/100 ml of the total dose (first day) 1/10 ml of the total dose (second day)	24 hours	1/100 ml (first day) 1/10 ml (second day)	Not notified	2
	Seitz 2009 *(102)*	4	1–5-7.5–10-30 ml	1 hour	53.5 ml	4 hours	1
	Torres 2012 *(93)*	34	5–10-15 ml (first day) 20–30-50 ml (second day)	1 hour	100 ml	2 hours (first day) 2 hours (second day)	2 (a 1-week interval)
	Gracia-Bara 2019 *(103)*	137	5–20 ml (first day) 50–50 ml (second day)	1 hour	25 ml (first day) 100 ml (second day)	2 hours (first day) 2 hours (second day)	2 (a 1-week interval)
IHR/ NIHR	Lerondeau 2016 *(28)*	97	1/100 + 1/10 ml of the total dose	1 hour	1.1/100 ml of the total dose	1 hour	1
	Soria 2019 (37)	110	5–15-30 ml	2 hours	50 ml	4 hours	1
	Trautmann 2019 (67)	18	0.05—0.5–1-5–7.5–10-25 ml	30 min	49.05 ml	3 hours	1
	Vega 2019 *(97)*	30	100 ml	Single dose	100 ml	12 min	1

DPT: Drug Provocation Test; IHR: Immediate Hypersensitivity Reaction; NIHR: Delayed Hypersensitivity Reaction.

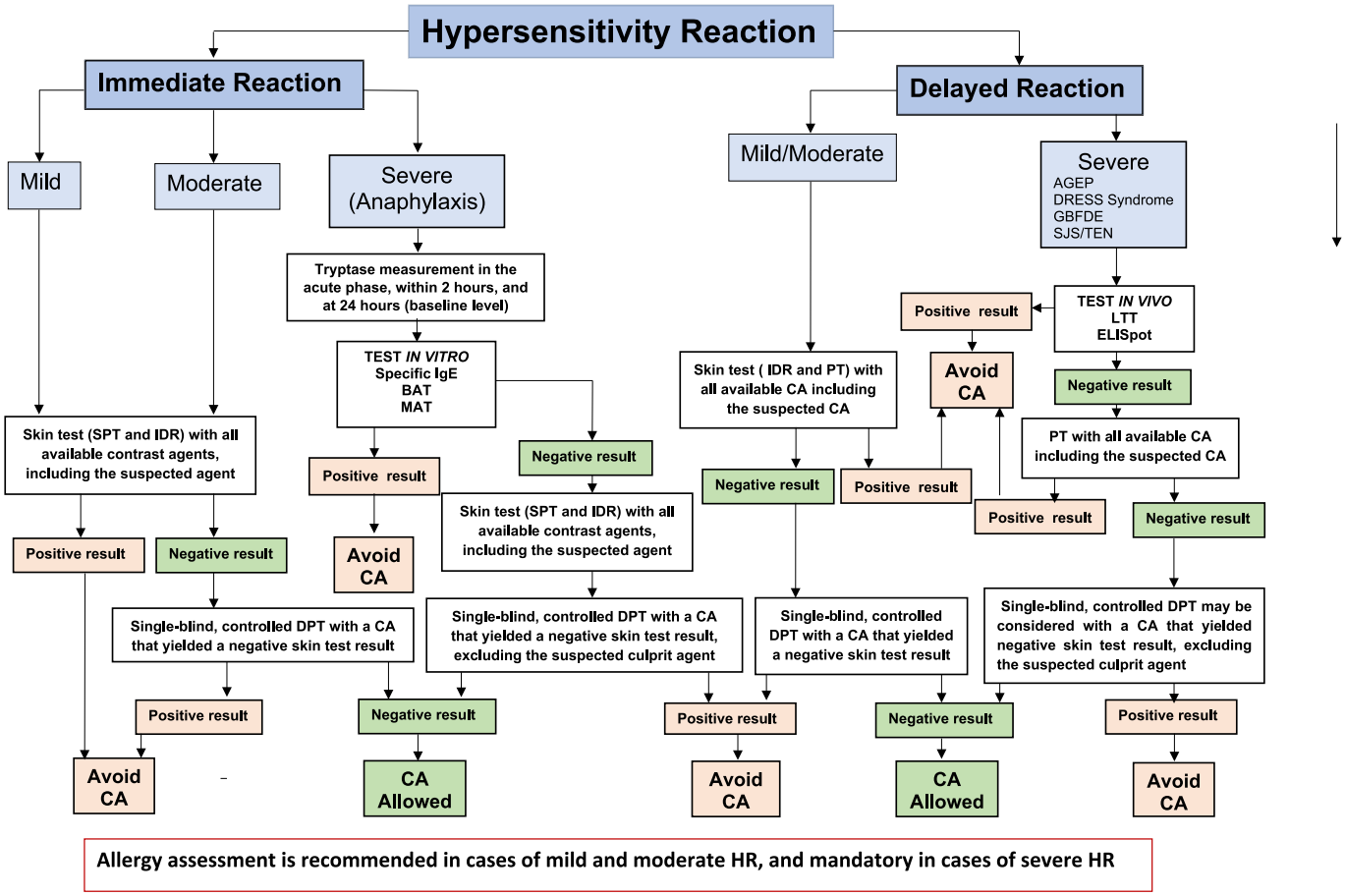

Fig. 3. Algorithm for the allergological assessment of immediate and non-immediate hypersensitivity reactions to contrast agent. AGEP: Acute Generalized Exanthematous Pustulosis; BAT: Basophil Activation Test; CA: Contrast Agent; DPT: Drug Provocation Test; DRESS syndrome: Drug Reaction with Eosinophilia and Systemic Symptoms; GBFDE: Generalized Bullous Fixed Drug Eruption; HR: Hypersensitivity Reaction; IDR: Intradermal Test; LTT: Lymphocyte Transformation Test; MAT: Mast Cell Activation Test; PT: Patch Test; SJS/TEN: Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis; SPT: Skin Prick Test.

examination.

This discrepancy in tolerance to a CA may be related to the fact that slow DPT might not adequately assess the involvement of mast cell activation mechanisms independent of IgE, such as activation through the mast cell receptor MRGPRX2. The activation of this receptor depends on the tissue concentration of the drug and, therefore, on the infusion rate of the CA [105].

To address this limitation, DPT at higher flow rates have been developed for both ICM (100 ml of ICM administered continuously over 12 min) and GBCA (dose adjusted to weight, administered continuously over 8 min). These protocols demonstrated excellent safety, with good tolerance observed in subsequent contrast-enhanced examinations in all patients using the recommended CA [95,106]. These same findings were confirmed in a later study using rapid DPT in a population of patients with a history of anaphylaxis to ICM [4]. Table 6 lists diverse DPT protocols with ICM published in recent years.

Finally, after describing the different diagnostic techniques required, an algorithm for the management of patients with a history of HR to CA is proposed (Fig. 3).

5. Conclusion

In the case of a HR to CA, both ICM and GBCA, performing an allergy study using *in vivo* and *in vitro* techniques helps improve the approach to such patients, following the recommendations of multiple studies and position papers or guidelines of the Scientific Societies. The appropriate diagnostic methodology allows us to safely confirm or exclude the occurrence of a true HR and the involvement of the suspected CA, as well as evaluating the tolerance to an alternative CA.

CRediT authorship contribution statement

Francisco Vega: Conceptualization, Supervision, Writing – original draft, Writing – review & editing, Investigation. **Aart J. van der Molen:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Maria Ruiz-Calatayud:** Writing – original draft, Writing – review & editing. **Aitana Alberdi:** Writing – original draft, Writing – review & editing. **Maria Catalá:** Writing – original draft, Writing – review & editing. **Carlos Blanco-Mota:** Writing – original draft, Writing – review & editing. **Annick A.J.M van de Ven:** Writing – review & editing. **José J. Laguna:** Writing – review & editing. **Carmen Sebastia:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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