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European Journal of Radiology 181 (2024) 111803

Contents lists available at ScienceDirect

European Journal of Radiology

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

Hypersensitivity reactions after diagnostic nonvascular administration of iodine-based contrast media and gadolinium-based contrast agents and the role of the drug allergy specialist

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ARTICLE INFO

Keywords:
Contrast media/administration and dosage
Drug administration routes
Hypersensitivity
Fluoroscopy
Tomography
X-ray computed
Magnetic resonance imaging

ABSTRACT

The risk of hypersensitivity reactions (HSR) following nonvascular administration of contrast media (CM) for diagnostic studies is very low, likely due to minimal absorption into the systemic circulation. Most published individual cases of HSR after nonvascular CM administration are immediate reactions caused by ionic high-osmolar CM, few by nonionic low-osmolar CM, and none by gadolinium-based contrast agents. Measures to prevent recurrent HSR following nonvascular administration are similar to those recommended to prevent HSR after intravascular CM administration. Premedication as preventive measure has been abandoned, while switching to an alternative CM, preferably based on the results of an allergological analysis, is increasingly advocated. In selected scenarios, preventive measures may be minimized.

1. Introduction

Despite the fact that the use of fluoroscopy [1] has diminished, many diagnostic studies with nonvascular contrast media (CM) administration are still performed on a daily basis. Nonvascular CM administration in the body can include gastro-intestinal (GI), urogenital, pancreaticobiliary, intraductal, intrathecal, or intra-articular routes. Iodine-based contrast media (ICM) are used much more frequently than gadolinium-based contrast agents (GBCA), whereby the old ionic high-osmolar contrast media (HOCM) are still in use [2]. Often, the CM is applied retrograde via a needle or catheter (Table 1).

Hypersensitivity reactions (HSR) are either immediate (IHR), occurring within 1 h of CM administration, or non-immediate (NIHR), occurring between 1 h and 1 week after CM administration (longer in some rare reactions). IHR can be either allergic (immunologic mechanism, often IgE-mediated) or nonallergic (direct activation of mast cell receptors, like Mas-Related G-Protein-coupled Receptor X2 (MRGPRX2) [3]. In NIHR, drug-specific T-cells play an important role, whereby in skin reactions a dermal infiltrate containing activated CD4 + or CD8 + T-cells and eosinophils can be found [4]. CM may not induce a primary immune response but can interact in multiple ways with receptors on memory T-cells activated by other substances (non-allergic NIHR) [3,5]. The gradation of reactions after intravascular CM by the American College of Radiology (ACR) into mild, moderate and severe reactions [6] may also be applied to HSR after nonvascular administration of CM [7].

The real-life incidence of HSR following the administration of intravascular nonionic ICM is 0.11–0.32 % [8,9], and following GBCA 0.007–0.015 % [10,11]. The evidence of HSR after administration of nonvascular CM for diagnostic imaging studies is limited to case series/reports (Table 2), and therefore the incidence appears to be too low for reliable estimations [2,12,13]. It is noteworthy that, unlike for intravascular administration, HOCM are still frequently used in nonvascular or intracavitary examinations. The reason for this continued use is that the possibility of CM absorption via transmucosal routes is very low, and thus HOCM are considered to have an appropriate safety profile. It should be realized that all CM can also induce HSR by a non-allergic IgE-independent mast cell activation, possibly via the MRGPRX2-receptors [14]. When using ionic CM, ions like meglumine can also cause HSR [15]. Furthermore, certain excipients of CM, like trometamol, may seldomly cause HSR [16].

All GBCA are registered for intravascular administration. Therefore,

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https://doi.org/10.1016/j.ejrad.2024.111803
Received 12 August 2024; Received in revised form 18 October 2024; Accepted 22 October 2024
Available online 24 October 2024

Abbreviations

ACR	American College of Radiology
BAT	Basophil Activation Test
CM	Contrast Medium/Media
CR	Cross-reactivity
DPT	Drug Provocation Test
EAACI	European Academy of Allergy and Clinical Immunology
ERCP	Endoscopic Retrograde Cholangiopancreatography
ESUR	European Society of Urogenital Radiology
EU	European Union
GI	Gastrointestinal
GBCA	Gadolinium-Based Contrast Agent/Agents
HOCM	High-Osmolar Contrast Media
HSG	Hysterosalpingography
HSR	Hypersensitivity Reaction/Reactions
ICM	Iodine-based Contrast Medium/Media
IDT	Intradermal Test
IHR	Immediate Hypersensitivity Reaction
LOCM	Low-Osmolar Contrast Media
LTT	Lymphocyte Transformation Test
MRGPRX2	Mas-Related G-Protein-coupled Receptor X2
NIHR	Non-Immediate Hypersensitivity Reaction
PEG	Poly-Ethylene Glycol
PT	Patch test
PTC	Percutaneous Transhepatic Cholangiography
RUP	Retrograde Uretero-Pyelography
SCAR	Severe Cutaneous Adverse Reactions
SJS	Stevens-Johnson Syndrome
SPT	Skin Prick Test
ST	Skin Test
TEN	Toxic Epidermal Necrolysis
VCUG	Voiding Cystourethrography

Table 1
Diagnostic examinations with nonvascular administration of CM in the body.

Nonvascular administration of ICM/GBCA for Diagnostic Use		
Fluoroscopy: ICM	***CT: ICM***	***MRI: GBCA***
Sialography	CBCT sialography	MR sialography
Gastro-intestinal tract	CT gastro-intestinal tract	MR gastro-intestinal tract
Urologic tract	CT urologic tract	MR urologic tract
Genital tract (HSG)		MR genital tract (vagina)
Arthrography	CT arthrography	MR arthrography
Myelography	CT myelography	MR myelography
Fistulography – sinography	CT fistulography – sinography	
Pancreatico-biliary (ERCP, PTC)		
	CT add-on to fluoroscopic examinations	

Abbreviations: CBCT = Cone-beam computed tomography; CT = computed tomography; ERCP = endoscopic retrograde cholangiopancreatography; GBCA = gadolinium-based contrast agents; HSG = hysterosalpingography; ICM = iodine-based contrast media; MR = magnetic resonance; MRI = magnetic resonance imaging; PTC = percutaneous transhepatic cholangiography.

Table 2
Types of contrast media involved in the 30 individual cases of hypersensitivity reactions described in this review.

Type of Administration	Ionic HOCM	Nonionic LOCM	GBCA
Gastrointestinal	IHR 4 Non-severe NIHR 2 SCAR 1	Non-severe NIHR 1 SCAR 1	–
Urologic	IHR 6	IHR 1	–
Genital	IHR 4	IHR 2	–
Pancreaticobiliary	IHR 1	Non-severe NIHR 1	–
Salivary duct	Non-severe NIHR 1	Non-severe NIHR 1	–
Intra-articular	IHR 1	IHR 1 SCAR 1	–
Fistulography	–	SCAR 1	–

Abbreviations: GBCA = gadolinium-based contrast agent; HOCM = high-osmolar contrast medium; ICM = iodine-based contrast medium; IHR = immediate hypersensitivity reaction; LOCM = low-osmolar contrast medium; NIHR = nonimmediate hypersensitivity reaction; SCAR = severe cutaneous adverse reaction

all nonvascular administrations are considered off-label indications. One exception is the use of specific diluted GBCA-formulations like Artirem® or Magnevist 2 mmol/L® that have been registered in selected European Union (EU) countries for MR Arthrography.

The objective of this narrative review is to provide an update on the current knowledge regarding HSR after the administration of CM using alternative routes to intravascular administration. A novel aspect of this review is to propose recommendations to prevent the recurrence of HSR in patients with a previous HSR to CM, and the role of the drug allergy specialist (or allergologist) therein. Barium and the old, discontinued superparamagnetic iron oxide-based (Lumirem®, Gastromark®, Abdoscan®, FerriSeltz®) or manganese-based (Lumenhance®) high- or low-signal intensity MRI agents are not discussed. Also, specialized neutral low-density oral CM developed for use in CT or MR of the bowel, like Volumen® or Lumentin®, as well as sorbitol, mannitol or polyethylene glycol (PEG) agents or vaginal gels, are not (purely) ICM- or GBCA-based and were excluded.

2. Gastro-intestinal administration

In recent years, the use of fluoroscopy of the GI system is rapidly declining for the stomach and bowel, but swallowing studies and oesophagography with ICM remain relatively widely used [1]. Similarly, due to the high spatial resolution and image quality of modern CT scanners, the need to use of ICM to opacify and/or distend the stomach and bowel is decreasing in favour of no distention or distention by water [17]. For dedicated CT enterography protocols low-density agents like mannitol, PEG, or the specialized agents are employed.

High-attenuation (positive) gastro-intestinal ICM can be administered either via oral intake, via a nasogastric or nasoduodenal tube, or via rectal administration through a rectal canula [18]. Nonionic low-osmolar ICM (LOCM) are nowadays routinely applied, if necessary in adequate dilutions (e.g., 1:20 for bowel opacification in CT). For iohexol there is a gastrointestinal preparation version available in the USA, while in a few EU countries there is a specific gastrointestinal preparation of iopamidol available [19]. The older ionic HOCM sodium meglumine diatrizoate, lysine diatrizoate, and meglumine ioxithalamate can still be used for diagnosis in the gastro-intestinal system but differ in palatability [20].

In CT examinations, ICM are usually administered both intravenously and orally/rectally in diluted form, and as a result the true incidence of HSR after gastro-intestinal ICM administration in CT is difficult to distinguish. Small amounts of ICM will be slowly absorbed by the GI mucosa (less than 2 %) with relatively more absorption in the upper than in the lower part of the GI tract [21–23]. Therefore, also oral

Table 3
Specific data on the 30 hypersensitivity reactions after nonvascular CM administration in this review.

Patient	Sex	Age	Type of administration	Culprit CM	Reaction	Other Relevant Information	Reference
1	F	64	Gastrointestinal (oral)	Sodium meglumine diatrizoate (diluted)	Severe IHR with respiratory distress, stridor, wheezing, desaturation		25
2	F	82	Gastrointestinal (oral)	Sodium meglumine diatrizoate (diluted)	Severe IHR with wheezing, tachycardia, tachypnoea. Recurrent similar severe IHR upon re-administration	Required ICU admission	26
3	M	58	Gastrointestinal (oral)	Sodium meglumine diatrizoate (diluted)	Severe IHR with laryngeal oedema, respiratory distress requiring cricothyroidotomy after unsuccessful intubation attempts		27
4	M	83	Gastrointestinal (oral)	Sodium meglumine diatrizoate (diluted)	NIHR with generalised erythema and mouth ulcers		28
5	M	39	Gastrointestinal (oral)	Sodium meglumine diatrizoate (diluted)	IHR with urticaria		28
6	M	62	Gastrointestinal (oral)	Sodium meglumine diatrizoate (diluted)	NIHR with maculopapular exanthema		28
7	NA	NA	Gastrointestinal (oral)	Iopamidol	NIHR with maculopapular exanthema	Iobitridol was well-tolerated	29
8	M	36	Gastrointestinal (oral)	Sodium meglumine diatrizoate (diluted)	Initially skin rashes and pruritus. Upon re-administration SCAR with erythema and vesiculobullous skin changes (TEN)	Needed treatment in burn centre.	31
9	F	63	Gastrointestinal (oral)	Iohexol (diluted)	SCAR with urticarial rash, oedema of forehead and periorbital region, haemorrhagic bullae (probable SJS/TEN)	Also, intravascular iopamidol administration	32
10	F	5	Urologic (VCUG)	Sodium diatrizoate and sodium acetrizoate	IHR with urticaria		43
11	M	9	Urologic (VCUG)	Sodium iothalamate 50 %	IHR with generalized urticaria		44
12	F	39	Urologic (RUP)	Methiodal 20 %	IHR with shortness of breath and wheezing	Previous HSR	45
13	M	38	Urologic (RUP)	Meglumine iothalamate	severe IHR with hypotension and ventricular fibrillation	Previous severe IHR found in patient records in other hospital	45
14	NA	2	Urologic (VCUG)	Meglumine iothalamate	mild urticarial skin rash		46
15	M	55	Urologic (VUE)	Meglumine iothalamate	temporary hypotension		46
16	F	19	Urologic (RUP)	Iohexol	Severe IHR with urticarial rash and progressive dyspnoea, requiring intubation and ICU-admission	Previous severe HSR with failed premedication before current examination	47
17	NA	NA	Urologic (Loopogram)	Low-osmolar ICM	Severe IHR with unresponsiveness and severe hypotension	Failed premedication	48
18	F	NA	Genital (HSG)	Meglumine diatrizoate	Severe IHR with urticaria and syncope		57
19	F	NA	Genital (HSG)	Meglumine metrizoate	IHR with urticaria		58
20	F	27	Genital (HSG)	Sodium meglumine diatrizoate	IHR with diffuse erythema, angioedema, stridor, and wheezing	History of seasonal rhinitis and asthma	59
21	F	23	Genital (HSG)	Meglumine ioxithalamate	Severe IHR with anaphylactic shock		60
22	M	65	Pancreatobiliary (ERCP)	Meglumine iothalamate	IHR with macular exanthema and pruritus		70
23	F	65	Sialography	Ioxaglate 320	NIHR with maculopapular exanthema		76
24	F	33	Sialography	Iodixanol 270	NIHR with marked swelling of the floor of the mouth and pharynx		77
25	F	27	Arthography	Iohexol	Mild IHR consisting of itching in the eye and periorbital angioedema	Allergy to house dust (mites)	85
26	NA	NA	MR arthrography	Mixture of lidocaine, meglumine diatrizoate, and diluted gadopentetate	Severe IHR with erythema, chest tightness, light-headedness, and brief loss of consciousness		86
27	F	53	CT arthography	Iodixanol	SCAR with acute generalized exanthematous pustulosis		87
28	M	57	Myelography	Metrizamide 170	NIHR with facial angioedema		99
29	M	19	Myelography	Iohexol 300	Severe IHR with laryngeal oedema		100
30	F	79	Fistulography	Iobitridol	SCAR with acute generalized exanthematous pustulosis	No cross-reactivity	105

Abbreviations: CM = contrast media; ICU = intensive care unit; ERCP = endoscopic retrograde cholangiopancreatography; F = Female; HSG = hysterosalpingography; IHR = immediate hypersensitivity reaction; M = Male; NA = not available; NIHR = nonimmediate hypersensitivity reaction; RUP = retrograde uretero-pyelography; SCAR = severe cutaneous adverse reaction; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; VCUG = voiding cysto-ureterography; VUE = video urodynamic examination.

ICM can elicit HSR of all severities, both IHR and NIHR. There is no convincing data that inflammation or ischemia of the bowel walls lead to more HSR.

In animal studies, sodium meglumine diatrizoate caused a large fluid shift into the bowel and epithelial damage of the bowel mucosa. This can explain the frequent diarrhoea with nausea and vomiting when using HOCM. Such effects are much less prominent when using a LOCM [24].

Three severe [25–27] and four non-severe [28,29] HSR cases have been published, that are presented in detail in Table 3. It should be noted that when HOCM is used orally and there is a non-protected airway, there is a risk of aspiration which may lead to pulmonary oedema, which may even be lethal [30].

Oral CM has been suspected as a probable cause of delayed severe cutaneous adverse reactions (SCAR) in two more cases [31,32], presented in Table 3.

Some reports describe isolated small bowel angioedema as an HSR, but no allergology studies were performed to support that the (CM-induced) bowel wall swelling was indeed angioedema. It is more

frequently caused by intravascular administration of CM and may be mediated via the gut-associated lymphoid tissue in the bowel wall [13,33]. This presumed angioedema is significantly underdiagnosed as it results in atypical abdominal discomfort or nausea and can resemble a chemotoxic reaction to ICM [34–36].

Gadolinium-based contrast agents (GBCA) and many other oral non-gadolinium CM (water, air, fruit juices, iron oxides, mannitol, PEG) have been tested over the years as oral/rectal CM for specific MRI-indications like MR cholangiopancreatography, MR enterography, or MR colonography. However, very few have made it to clinical application, and many products (e.g., Magnevist Enteral®, Gadolite®) have been withdrawn from the EU markets.

Nowadays, GBCA are very rarely used for gastrointestinal purposes, but have been used incidentally in patients with previous (severe) HSR to ICM in the past [37,38]. These GBCA can also be absorbed by the gastrointestinal mucosa in small amounts. Given the very low incidence of hypersensitivity reactions to intravascular GBCA, the risk of inducing such reactions via the gastro-intestinal route is largely theoretical.

3. Urologic administration

ICM, including older HOCM, are used since the invention of radiographic CM for a variety of fluoroscopic procedures such as (CT) voiding cystourethrography (VCUG), retrograde uretero-pyelography (RUP), nephrostomography, urodynamic examinations, and retrograde urethrography. CM may be used to a lesser degree to assist newer endourologic procedures such as JJ-tube or stent placements. Nowadays, LOCM are the mainstay for fluoroscopic procedures, often using optimized concentrations (140–240 mgI/ml).

ICM are absorbed by the urothelium with a potentially higher rate if ICM is injected under pressure or if drainage of CM is slow. In studies with ionic HOCM on RUP, this resorption was on average 6.9 % with sodium iothalamate and mainly took place in the pelvicalyceal systems but not in the ureters [39]. In bladders of children undergoing VCUG, ionic HOCM were absorbed if the ICM remained in the bladder for 15 min or longer but did not occur when voiding was complete [40]. Injection of undiluted ionic HOCM in bladders of dogs can elicit an inflammatory response in bladder mucosa, mainly related to osmolality and salt concentration [41]. When testing nonionic LOCM, such effects could not be reproduced [42].

Urologic CM administration can also elicit HSR of variable severity. In the majority of these ionic HOCM have been used [43–46], while a HSR after use of nonionic LOCM [47,48] is rare (details in Table 3).

In a survey among members of the Society of Endourology, despite a low response rate, almost a third of respondents had experienced at least one HSR after urologic administration [49]. The incidence of HSR after urologic administration using ionic HOCM has been estimated at 0,26 % [45]. In contrast, in a series of 11,714 video-urodynamic examinations, in which the majority was performed using iohexol 140 mgI/ml, no severe HSR could be demonstrated, but mild-moderate reactions were not reported [50]. In a large analysis on administrative data of hospitalized patients, a relatively high adverse reaction rate of 0,48 % was recently reported [51].

GBCA are almost never used in urologic procedures. GBCA has been used in CT cystography or urethrography in patients with previous (severe) HSR to ICM [52,53]. Recently, contrast-enhanced MRI with an intravesical GBCA-mixture has been suggested a useful tool for bladder cancer surveillance [54]. There is no available data on HSR associated with off-label urologic GBCA use.

4. Genital administration

For evaluation of the uterine cavity and tubal patency in infertility, the obstetric world is moving from hysterosalpingography (HSG) to hysterosalpingo-foam-sonography. HSG is routinely performed with oil-soluble (Lipiodol UF®) or water-soluble CM [55,56], and in this review we focus on HSR for water-soluble ICM. In HSG, exposure to ICM is via direct contact in the uterus and fallopian tubes, via venous/lymphatic intravasation, or via peritoneal spillage [56].

During HSG, most patients have pain and discomfort, but HSR are rare [57–60] (details in Table 3). In multiple studies (partly) using nonionic LOCM for HSG, no HSR were demonstrated [61–63]. A recent survey in The Netherlands with over 5165 patients revealed no anaphylactic reactions, and only two HSR (0.1 %) after water-soluble CM, but neither the causative CM nor the reactions were specified. The majority of centres used nonionic LOCM [64].

In some centres, MR-HSG using GBCA has been performed with good results [65]. Rarely, GBCA have also been used for conventional HSG in patients with previous (severe) HSR to ICM, but the dose needed is relatively high [66,67]. No HSR after intrauterine administration of GBCA has been published.

5. Pancreaticobiliary administration

Pancreaticobiliary administration of ICM is part of T-tube cholangiography during surgery, endoscopic retrograde cholangiopancreatography (ERCP), and percutaneous transhepatic cholangiography (PTC). Studies with cholangiographic HOCM, like iopanoic acid, were not considered.

Renal excretion of CM has been detected after ERCP, even in the absence of pancreatitis, showing that systemic absorption can occur [68,69]. Therefore, pancreaticobiliary procedures may also elicit HSR to ICM [70] (details in Table 3). A 55-year old woman with recurrent cholangitis in a liver transplant developed a NIHR with diffuse pruritic erythema 1–6 days after intravascular iomeprol administration, that re-occurred after ERCP despite switching to nonvascular iohexol administration and premedication with corticosteroids (EM Hutten and AAJM van de Ven, personal communication).

In a retrospective analysis of 601 ERCPs using meglumine iothalamate in patients with perceived risk factors for adverse reactions, no adverse reaction was seen [71]. In another retrospective analysis of 2295 ERCPs in patients with previous HSR to ICM, no anaphylactoid or severe adverse reaction occurred [72].

The risk of HSR is very low, even in patients at high-risk for HSR. Still, GBCA have been administered for ERCP in such patients, but with conflicting results [73,74]. No HSR from pancreaticobiliary administration of GBCA has been published.

6. Salivary duct administration

Conventional or cone-beam CT sialography is relatively commonly used to study the parotid and submandibular salivary ducts. ICM are used for sialography, if needed extended with cone-beam CT. As the CM is absorbed [75], HSR can occur [76,77] (details in Table 3).

A recent review of 1515 cone-beam CT sialograms showed no hypersensitivity reactions [78].

Sialography with GBCA has been used in patients with previous HSR to ICM [79,80]. No HSR has been published with salivary duct administration of GBCA. However, nowadays non-contrast MR Sialography has supplanted this, especially for the diagnosis of Sjögren's syndrome and sialadenitis [81].

7. Intra-articular administration

ICM are routinely used for single/double-contrast (CT) arthrography and to help establish needle placement before MR arthrography.

Small amounts of intra-articular administered ICM can be absorbed by the synovium [82].

In a survey of 126,000 arthrography examinations from the HOCM era, urticaria (both as IHR and NIHR) were reported in 61 patients (0,05 %) and hypotension or laryngeal oedema with collapse in 5 patients (0,004 %) [83]. A follow-up survey with 262,000 arthrography

examinations, using a mix of HOCM and LOCM and including 13,320 MR arthrograms, reported 776 immediate and 171 delayed cases of urticaria (0,36 %) and 8 anaphylactic reactions (0,003 %) [84]. Individual patients with HSR have also been described [85–87] (details in Table 3).

In MR arthrography, very diluted GBCA are used (2 mmol/L or a 1:250 dilution), often using specific GBCA-formulations. These may be mixed with small amounts of ICM for fluoroscopic monitoring of correct intra-articular needle placement. Trace amounts of GBCA can also be absorbed, but due to the dilution the number of HSR following MR arthrography is almost non-existent [88].

8. Intrathecal administration

CM can be administered via intrathecal (IT) route for diagnostic conventional myelography (CM), CT-myelography (CTM), and MR-myelography or MR-cisternography (MRMC). The indications and details of the procedure have been described in detail in specific CM/CTM [89–91] and MRMC reviews [92,93], as well as in the latest ACR-ASNR-SPR Practice Parameter [94]. Interventional or therapeutic applications, such as for specialized pain medicine procedures will not be considered here.

Pharmacovigilance and case reports have showed that accidental IT administration of ionic HOCM can cause severe toxic adverse reactions, most commonly presenting as ascending tonic-clonic seizures, which may even be fatal, but HSR are rare [95,96]. Since the 1980s, LOCM have been primarily used for IT administration, and HSRs following their use are extremely rare, with iopamidol being the most extensively studied. Multiple small comparative studies with metrizamide, iohexol, and iopamidol demonstrated excellent safety profiles without significant HSR. Large studies on IT CM administration, each including more than 1,000 patients, have confirmed the findings of earlier comparative studies, reporting no cases of HSR [97,98]. However, some case reports have documented HSR following IT CM administration [99,100] (details in Table 3).

In three successive GBCA safety studies using IT gadobutrol, employing doses of 0.1–0.5 mmol to study the glymphatic system in patients without a history of a previous HSR, only non-serious neurotoxic events were demonstrated, but no HSR [101–103]. Similarly, a *meta*-analysis of 53 studies involving 1,036 patients found that adverse events following intrathecal GBCA administration occurred in 13 % of cases, with all reported events being neurotoxic and more severe associated with doses greater than > 1 mmol, while no HSR could be demonstrated [104].

9. Miscellaneous administrations

Fistulography/sinography, often in combination with CT, is used for diagnosis and delineation of entero-cutaneous fistulae, abdominal sinus, and abscesses. One case of acute generalized exanthematous pustulosis after fistulography with iobitridol has been published [105] (Table 3).

Concluding, the risk of HSR after nonvascular CM administration is very low, likely due to minimal absorption into the systemic circulation. Most reported individual HSR in this review have been caused by ionic HOCM followed by nonionic LOCM, especially during gastro-intestinal or urogenital administration. No HSR have been reported after nonvascular use of GBCA. Underreporting will be an issue for all CM.

10. Prevention of recurrent hypersensitivity reactions

There are no clear guidelines on the management of patients with a history of HSR to CM that are scheduled for nonvascular CM administration. Despite its rarity, the European Society of Urogenital Radiology (ESUR) guidelines advise that the same recommendations should be followed for intracavitary administration of CM as for intravascular administration in the case of HSR to CM, regardless of the route through which the reaction was induced [106].

Table 4
Classification of contrast agents for non-vascular administration according to the chemical characteristics of their molecules.

	IODINE-BASED CONTRAST MEDIA (ICM)	
GROUP	**MOLECULE**	**CHARACTERISTICS OF THE MOLECULE**
	Group A	
Ionic ICM	Diatrizoate meglumine/sodium	Contain meglumine
	Ioxithalamate meglumine	
	Group B	
Nonionic ICM	Iohexol	Contain a basic carbamoyl sidechain
	Ioversol	
	Iomeprol	
	Iodixanol	
	Group C	Contains a methylated carbamoyl sidechain
	Iobitridol	
	Group D	Contains both a basic carbamoyl sidechain and a methylated carbamoyl sidechain
	Iopromide	
	Group E	
	Iopamidol	Do not contain any type of carbamoyl sidechain
	Iosarcol	
	GADOLIUM-BASED CONTRAST AGENT (GBCA)	
Linear GBCA*	**Group F**	Contains meglumine
	Gadobenate dimeglumine	
	Group G	Does not contain meglumine
	Gadodiamide	
Macrocyclic GBCA	**Group H**	Contains meglumine
	Gadoterate meglumine	
	Group I	Do not contain meglumine
	Gadoteridol	
	Gadobutrol	

*Linear GBCA registrations are limited or only allowed for specific indications in Europe.
Abbreviations: GBCA = gadolinium-based contrast agent; ICM = iodine-based contrast medium.

Different strategies have been defined to prevent the recurrence in patients with previous HSR [6,107–109], which are described below:

- *Choosing an Alternative Imaging Modality*

A first approach could be using an alternative imaging modality that does not require a CM of a similar class that caused the HSR (e.g., GBCA or ultrasound contrast agent instead of ICM), or one can consider performing the examination without CM. Even when an alternative imaging modality is not available, or if this does not maintain acceptable diagnostic quality for proper patient management, the patient should never be denied a well-indicated examination. In all cases, communication with the referring specialist is recommended.

- *Use of premedication*

Traditional protocols of premedication with H1-antihistamines and corticosteroids have been used since the era of HOCM and continue to be widely utilized [110,111]. Premedication may decrease the incidence of HSR, mainly by reducing the number of mild reactions [112], but without significant impact on severe HSR [113].

The current evidence regarding the efficacy of premedication is highly heterogeneous and of low quality [114,115]. The ACR Manual still recommends its use [6], despite recent publications from influential working groups questioning its true utility [116,117]. In contrast, there is in Europe a clear stance against the use of premedication [118], and, according to the EAACI guideline, it could only be used as an adjunct in the case of administering an alternative CM when the responsible agent is unknown, and in no case for NIHR [108].

Table 5
Empirical choice of an alternative contrast agent based on the characteristics of their molecules (composition of group A − I according to Table 4).

INVOLVED CM	ALTERNATIVE CM FOR NON-VASCULAR ADMINISTRATION	
	Lower Risk	**Higher Risk**
ICM Group A	ICM Groups B, C, D, E GBCA Group G, I	GBCA Groups F, H
ICM Group B	ICM Groups A (lowest), C, E All GBCA	ICM Group D
ICM Group C	ICM Groups A (lowest), B, E All GBCA	ICM Group D
ICM Group D	ICM Groups A (lowest), E All GBCA	ICM Groups B, C
ICM Group E	ICM Groups A (lowest), B, C, D All GBCA	
Unknown ICM (the most likely CM would be Group A or iohexol)	ICM Groups C, D, E GBCA Groups G, I	ICM Groups A, B, D GBCA Groups F, H
GBCA Group F*	GBCA Groups G, I ICM Groups B, C, D, E	GBCA Group H ICM Group A
GBCA Group G*	GBCA Groups F, H, I All ICM	
GBCA Group H	GBCA Groups G, I ICM Groups B, C, D, E	GBCA Group F ICM Group A
GBCA Group I	GBCA Groups F, G, H All ICM	
Unknown GBCA	ICM Groups B, C, D, E	All GBCA

*Linear GBCA registrations are limited or only allowed for specific indications In Europe.
GBCA = gadolinium-based contrast agent; ICM = iodine-based contrast media.

- *Empiric change of the specific contrast agent*

Changing the culprit ICM has emerged as the preferred preventive strategy, proving to be superior in preventing HSR compared with premedication [116,119,120]. Data on changing GBCA are more limited but indicate a similar decrease in the rate of HSR [121–123]. Although in theory there is nearly always a safe, not cross-reacting alternative CM available, practice can be more challenging as both the variability of the cross-reactivity (CR) and the availability of the CM in real-practice [107,124,125] complicates the selection of a safe alternative, especially when the implicated CM is unknown. To facilitate the selection, diverse classifications of CM based on their chemical differences have been developed [124,126–128].

Following one of the latest publications, we propose a classification of both types of CM [128](Table 4): if the CM responsible for a previous HSR is an ionic ICM or GBCA, the best option would be to recommend a nonionic agent, which is likely to be well tolerated due to structural differences between the two groups. It is important to note that meglumine has been shown to induce non-allergic HSR through mast cell activation via MRGPRX2 [14,129]. Therefore, the use of certain ionic linear GBCA (gadopentate dimeglumine and gadobenate dimeglumine) and macrocyclic GBCA (gadoterate meglumine) should be avoided, as they share the presence of meglumine with ionic CM. If the implicated agent is a nonionic ICM, an ionic ICM can be used for nonvascular use. The presence of a N-(2,3-dihydroxypropyl) carbamoyl sidechain appears to be relevant for cross-reactivity [130]. With this criterion, a change to an ICM without this sidechain or with a modified carbamoyl sidechain may reduce subsequent HSR, whereas switching to an agent with the same sidechain may be risky.

The CR between linear and macrocyclic GBCA appears to be very low, while the CR seems to be higher among macrocyclic GBCA [131]. The current European restriction on the use of linear GBCA complicates a change from macrocyclic to linear GBCA.

To select a safe alternative, we have proposed a selection system (Table 5) based on both 2D and 3D chemical similarities and previous tolerance data among the different CM [128]. However, an empiric change of CM remains inferior to a change of CM based on an allergological analysis, as most studies on CR do not allow the choice of the safest CM on a robust scientific basis.

11. Allergological evaluation by the drug allergy specialist / allergologist

The best way to evaluate CR and to choose safe alternative CM is to base the selection on the results of an allergy analysis, whose diagnostic tools are listed below.

11.1. In vitro test

In vitro tests can improve diagnostic evaluation without exposing the patients, but this type of testing is only performed in specialized centres.

The main techniques available are:

- Basophil Activation Test (BAT)

In IHR to CM, BAT is particularly useful in cases with severe reactions or when ST or DPT are contraindicated [132]. This technique shows a good correlation with in vivo tests, with acceptable levels of sensitivity and excellent specificity for GBCA [133] and ICM [134]. BAT is considered an additional tool for patients with IHR who have severe reactions or those at high risk during in vivo testing, according to EAACI practice guidelines [108]. BAT has limitations, as it may not adequately assess reactions to CM mediated by MRGPRX2, since this mast cell receptor is underrepresented in basophils [135].

- Lymphocyte Transformation Test (LTT)

In NIHR to CM, a LTT should not be conducted during the acute stage, but rather 4–8 weeks after remission. The diagnostic value of LTT in NIHR is unclear, as the negative predictive value of LTT is unknown. If available, it may be used as an additional diagnostic tool in selected cases where ST is contraindicated [108].

11.2. Skin test (ST)

The first approach would be to perform ST, which have been considered a valuable diagnostic tool to confirm reactive CM and help identify alternative CM without CR [108,124]. ST must be performed with the broadest possible panel of CMs, including the one involved in the reaction (if known), preferably within 2–6 months after the reaction to improve the efficiency of the study [108]. All skin testing should adhere to EAACI standards, starting with the skin prick test (SPT) and, if negative, continuing with the intradermal test (IDT) [136]. For SPT, the CM should be used undiluted and diluted at 1:10 for the initial IDT, with additional IDT using undiluted CM if previous tests are negative. However, results should be interpreted with caution due to the increased risk of false positives [109,137].

Although positive SPT have been reported, most cases have been positive in IDT [137], with delayed IDT readings being the most sensitive diagnostic tool for NIHR [108,138]. In IHR, a positive ST indicates that the patient is sensitized to the CM, increasing the possibility of a more severe IHR, as they are more likely to be IgE-mediated allergic HSR [132].

The negative predictive value of ST is high, especially in the case of IHR [139,140]. For SCAR, testing should be delayed for more than 6 months, prioritizing patch tests (PT) with delayed readings at 48–96 h over IDT with delayed readings to decrease the risk of systemic reactions [108]. When selecting an alternative CM for a radiological examination,

Table 6
Recommendations for Nonvascular ICM or GBCA Administration (See also Online Supplement 1–2).

Following nonvascular ICM or GBCA administration, small amounts of ICM or GBCA can be absorbed through mucosal surfaces and enter the systemic circulation.
Hypersensitivity reactions after nonvascular administration of ICM and GBCA may occur, but their incidence is very low.
Refer patients who have experienced a previous *moderate to severe* hypersensitivity reaction to ICM or a *severe* hypersensitivity reaction to GBCA to a drug allergy specialist for an allergological evaluation.
In general, in patients who have experienced a previous hypersensitivity reaction to CM, similar preventive measures can be used prior to examinations using nonvascular CM administration as prior to examinations using intravascular CM administration.
Alternative CM should preferably be selected on the basis of an allergological analysis.
In patients that have experienced a previous hypersensitivity reaction to CM, premedication is not indicated prior to nonvascular CM administration.
Given the lack of hypersensitivity reactions following nonvascular GBCA administration, preventive measures may be minimized (empiric change of GBCA) before administering nonvascular GBCA in patients who have previously experienced a hypersensitivity reaction to GBCA.

it should preferably be one that previously tested negative in ST [108,118,131,141].

11.3. Drug Provocation Test (DPT)

DPT is the gold standard in the diagnosis of drug allergy. However, DPT is a laborious, high-risk procedure with the potential risk of iatrogenic anaphylaxis and should hence only be performed in selected patients by experienced personnel at specialized centres using only skin test negative CM. DPT can be useful both to verify the involvement of a CM in a previous HSR and to confirm the tolerance of an alternative CM, especially when safe alternatives cannot be identified using ST or BAT [108,142]. There are no standardized protocols for DPT with CM, limiting widespread use [143]. Published protocols include both classical drug administration schemes with incremental doses over 2–3 h [108] and rapid administration using high-flow rates of ICM or GBCA, closely resembling its administration in CT or MRI [144,145].

Due to the lack of HSR after nonvascular CM administration of GCBA, preventive measures may be minimized (empiric change of GBCA) before nonvascular administration of GBCA in patients that have experienced a previous HSR after GBCA administration, especially when healthcare costs need to be reduced or in areas with limited access to drug allergy specialists [146] (Table 6 – Online Supplement 1–2).

12. Conclusion

The risk of HSR after nonvascular CM administration for diagnostic studies is very low, likely due to minimal absorption into the systemic circulation. Most published individual cases have been caused after ionic HOCM and no cases after GBCA administration. Measures to prevent recurrent HSR are similar to those recommended to prevent HSR after intravascular CM administration. The use of premedication is currently minimized, and the focus is on switching to an alternative CM, preferably based on the results of an allergological analysis. Preventive measures may be minimized in selected scenarios.

CRediT authorship contribution statement

Aart J. van der Molen: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Francisco Vega:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization. **Annick A.J.M van de Ven:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization. **Ilona A. Dekkers:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **José J. Laguna:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis.

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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejrad.2024.111803.

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