Reazioni avverse ai mezzi di contrasto: dalla diagnosi ai challenge

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FATTORI DI RISCHIO

REVIEW Open Access

SIRM-SIAAIC consensus, an Italian document on management of patients at risk of hypersensitivity reactions to contrast media

Costantino *et al. Clin Mol Allergy* (2020) 18:13

EAACI POSITION PAPER

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

Practice parameters for diagnosing and managing iodinated contrast media hypersensitivity *Allergy*. 2021;76:1325–1339.

THE MOST SIGNIFICANT RISK FACTOR FOR HR TO A ICM IS A PREVIOUS REACTION.

BOTH IHR AND NIHR HAVE BEEN REPORTED TO OCCUR IN A FREQUENCY OF ABOUT 0.5%-3% OF PATIENTS RECEIVING NONIONIC ICM

(modificata)

Factors related to ICM reactions.

		p*
Gender	Female Male	< 0.01
Age (years)	< 65 ≥ 65	< 0.01
First exposure	Yes	< 0.01
Cardio-vascular disease	Yes	< 0.01
Respiratory allergy	Yes	< 0.01
Adverse Drug reactions	Yes	< .001

Hypersensitivity reactions to iodinated contrast media in Italy: a retrospective study. Characteristics of patients and risk factors

Eur Ann Allergy Clin Immunol 2022

Isn't it time to consider oncological status as a new risk factor of iodinated contrast media hypersensitivity?

Eur Ann Allergy Clin Immunol 2022

THE INCIDENCE OF IHS REACTIONS TO ICM WAS HIGHER IN PATIENTS WITH CANCER (2,1% VS 1,1% FOR PATIENTS WITH-OUT CANCER, P<0,001)

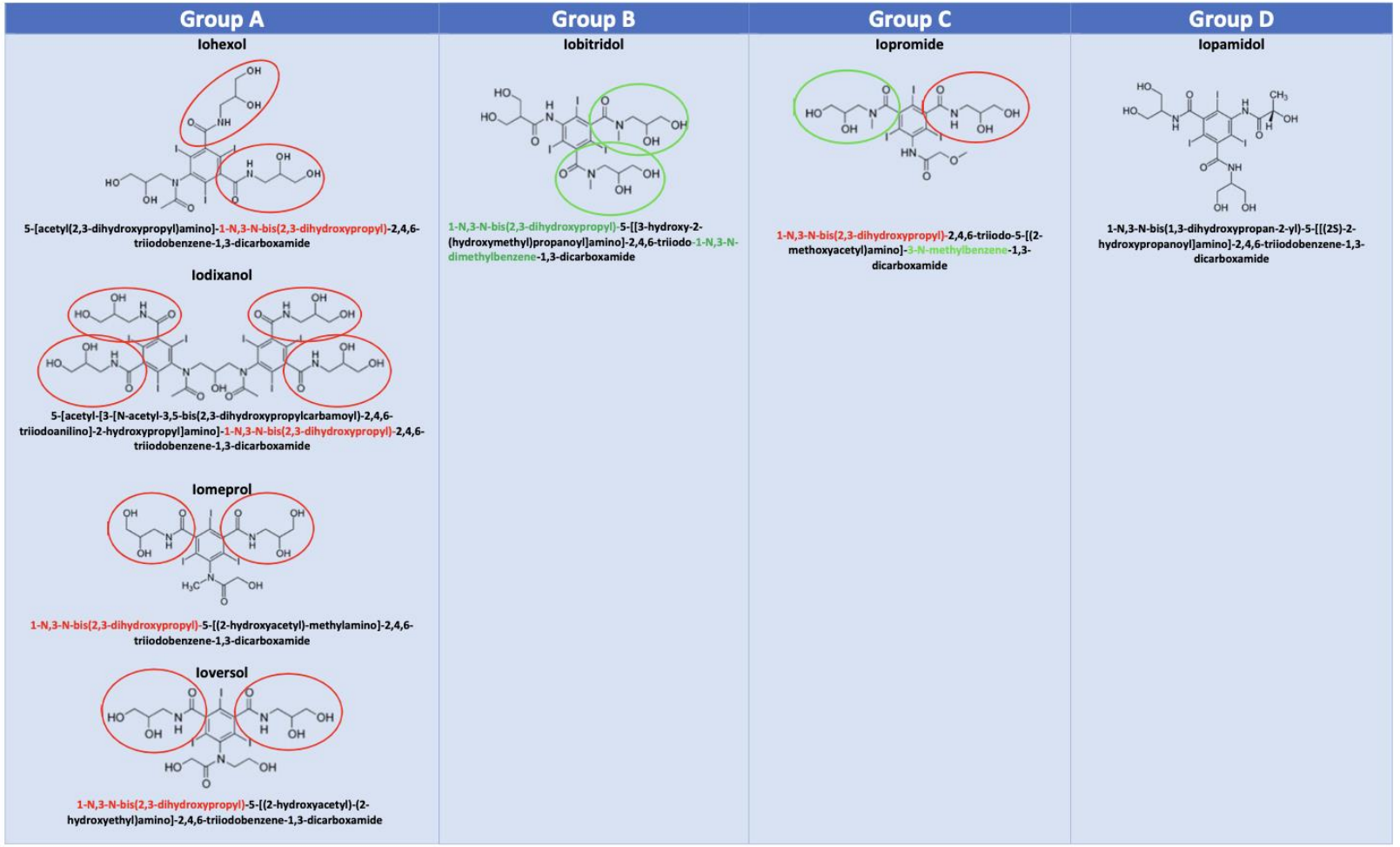


Fig. 1 Chemical formulas and comparison of molecule and benzene chain arrangements by colours. Position 1 and 3 of the benzene ring: Classic carbamoyl sidechain (1-N,3-N-bis(2,3-dihydroxypropyl) in red. Modified carbamoyl sidechain in green. Position 2, 4, 6 of the benzene ring: three iodine atoms. Position 5 of the benzene ring: highly variable side chains defining diverse types of ICM

Vega F, van de Ven AAJM, van der Molen AJ. Cross-reactivity in hypersensitivity reactions to contrast agents: new classification and guide for clinical practice. Eur Radiol. 2024 Dec;34(12):7583-7588. doi: 10.1007/s00330-024-10872-8. Epub 2024 Jun 27. PMID: 38937294.

REAZIONI AVVERSE AI MEZZI DI CONTRASTO

TOSSICHE/FISIOLOGICHE

CALORE
FLUSHING
SAPORE METALLICO
NAUSEA
VOMITO
PRURITO

IPERSENSIBILITÀ

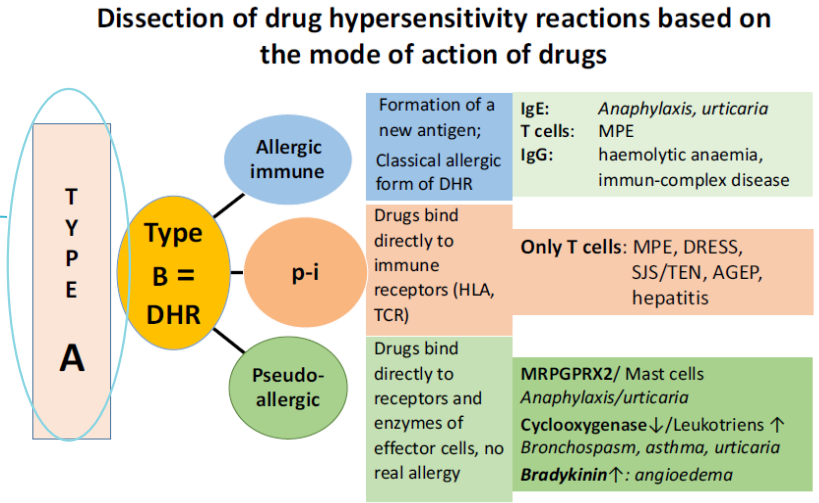


FIGURE 4 Classification of type B reactions (modified from 10): Adverse drug reaction are sub-classified as type A and B reactions.[1,2] Type B reactions correspond to DHR, which can be classified as *allergic/immune, p-i and pseudo-allergic reactions*.[10] Allergic/immune reactions are due to antigen formation and can lead to all types of Gell and Coombs-mediated immune reactions; p-i stimulations lead exclusively to T-cell reactions, which are unorthodox and sometimes severe. So-called pseudo-allergic reactions are heterogeneous and due to stimulation of inflammatory mechanism. They include MRGPRX2 stimulation of mast cells, inhibition of cyclooxygenase due to NSAID and of bradykinin metabolism in ACE therapy. *details see text

Immune pathomechanism and classification of drug hypersensitivity
Pichler WJ, Allergy 2019

REAZIONI DA IPERSENSIBILITÀ A MEZZI DI CONTRASTO

TIPI DI REAZIONE

Immediate (entro 1-6 ore)	Ritardate (dopo 1 ora)
IgE-mediate/Non IgE-mediate	**Cellulo-mediate**
Orticaria/angioedema*	Orticaria
Dolore addominale	Esantema maculo-papulare
Vomito	Eritema fisso da farmaco
Diarrea	SDRIFE
Broncospasmo*	DRESS
Ipotensione	AGEP
	S. Stevens Johnson

*esacerbazione patologia di base (asma, CSU)

Febbre ?

Brivido ?

Brockow et alK. Allergy to Radiocontrast Dye. Immunol Allergy Clin North Am. 2022 May;42(2):391-401.
Torres MJ et al Practice parameters for diagnosing and managing iodinated contrast media hypersensitivity. Allergy. 2021 May;76(5):1325-1339.
Broyles AD et al Practical Guidance for the Evaluation and Management of Drug Hypersensitivity: Specific Drugs. J Allergy Clin Immunol Pract. 2020 Oct;8(9S):S16-S116.
Liccardi et al Bronchospasm and iodinated contrast media (ICM): an accurate evaluation is mandatory. Eur Ann Allergy Clin Immunol. 2022 Jul 18.

TABLE 1 Type of drugs eliciting drug hypersensitivity by hapten, p-i or pseudo-allergic mechanism[a]

Hapten	p-i[b]	Pseudo-allergy
Beta-lactam antibiotics: penicillins, amoxicillin, flucloxacillin, cephalosporins, carbapenem, monobactam; penicillamine	*Beta-lactam antibiotics*: flucloxacillin, amoxicillin, cephalosporins; monobactam	
Sulphanilamides: sulphamethoxazole-NO[c]	*Sulphanilamides* sulphamethoxazole, sulfapyrdine and other sulphanilamides	
		NSAID acetylsalicylic acid, diclofenac, mefenamic acid, ibuprofen, etc.
Metamizole	*Metamizole*	*Metamizole*
Chinolones[d] (ciprofloxacin, moxifloxacin, norfloxacin,..)	*Chinolones* (ciprofloxacin, moxifloxacin, norfloxacin,..)	*Chinolones*[d] (ciprofloxacin, moxifloxacin, norfloxacin,..)
RCM[d] iomeprol, iodihexol and other radiocontrast media	*RCM*: iomeprol, iodihexol and other radiocontrast media	*RCM*: Iomeprol[d], iodihexol[d] and other radiocontrast media
Muscle relaxants[d] (rocuronium, suxamethylcholin, etc....		*Muscle relaxants*[d] (rocuronium, suxamethylcholin, etc....
	Vancomycin	*Vancomycin*
	Antiepileptics[b]: carbamazepine lamotrigine, phenytoin	
	Local anaesthetics: lidocain, mepivacain etc.	
	Allopurinol[b]*/oxypurinol*[b]	

Immune pathomechanism and classification of drug hypersensitivity
Pichler WJ, Allergy 2019

VELOCITÀ DI INFUSIONE

Relationship between Lower Dose and Injection Speed of Iodinated Contrast Material for CT and Acute Hypersensitivity Reactions: An Observational Study

Hyo Jung Park, MD • Jung Hee Son, MD* • Tae-Bum Kim, MD, PhD • Min Kyoung Kang, RPh, MS • Kyunghwa Han, PhD • Eun Hye Kim, RN, MS • Ah Young Kim, MD, PhD • Seong Ho Park, MD, PhD*

Abbreviation

CI = confidence interval

Summary

Reduction in the dose and injection speed of nonionic iodinated CT contrast material was associated with fewer acute hypersensitivity reactions.

Key Results

- The rate of acute hypersensitivity reactions was lower with use of a nonionic contrast material dose of 1.5 mL/kg and injection speeds of 2.5 or 3 mL/sec than with a dose of 2 mL/kg and injection speeds of 3 or 4 mL/sec (1.42% vs 1.86%, respectively).
- In adjusted analyses, lower contrast material dose and injection speed were associated with less frequent acute hypersensitivity reactions (relative risk, 0.85; $P = .03$).
- Lower contrast material dose and injection speed were related to a lower rate of moderate-to-severe hypersensitivity reactions (relative risk, 0.62; $P = .004$).

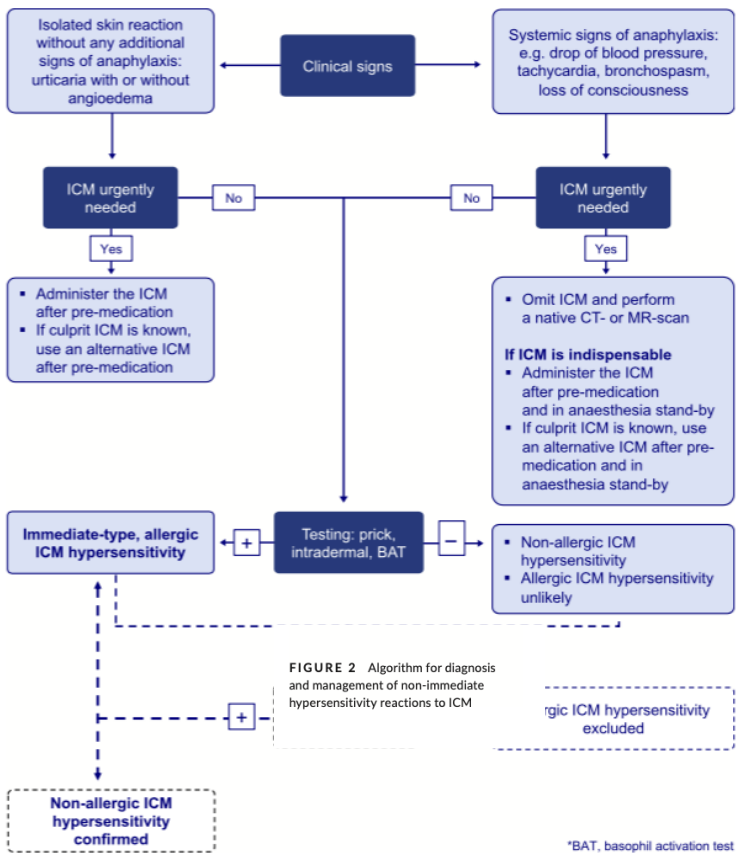
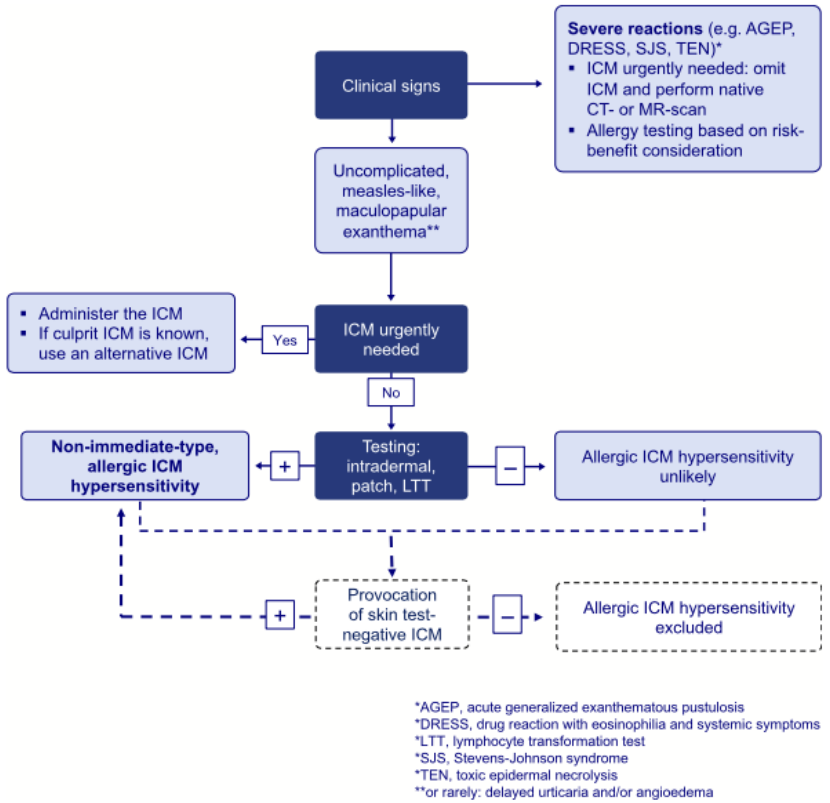


FIGURE 2 Algorithm for diagnosis and management of non-immediate hypersensitivity reactions to ICM

FIGURE 1 Algorithm for diagnosis and management of immediate hypersensitivity reactions to ICM

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



Torres MJ et all. Practice parameters for diagnosing and managing iodinated contrast media hypersensitivity. Allergy. 2021 May;76(5):1325-1339. doi: 10.1111/all.14656. PMID: 33170954.

Recommendations

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

Recommendations

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

- IDTS ARE GENERALLY CARRIED OUT AT 1:10 DILUTIONS FOR IHR AND NIHR, BUT UP TO 70% OF IDT REACTED TO THE *UNDILUTED* ICM WITH GOOD SAFETY WITHOUT GENERATING FALSE POSITIVE IDT AND IT MAY BE *USED IF* THE IMMEDIATE READING OF *THE 1:10 DILUTION IS NEGATIVE*

- IDT WITH UNDILUTED ICM MAY INDUCE IRRITATIVE LARGE UNCOLOURED WHEALS AFTER 20 MINUTES WITHOUT SURROUNDING ERYTHEMA, POSSIBLY DUE TO THE OSMOLARITY OF THE PRODUCTS, WHICH MAY BE DIFFICULT TO DISTINGUISH FROM POSITIVE IDT (LARGE WHEAL WITH A SURROUNDING ERYTHEMA)

Torres MJ et all. Practice parameters for diagnosing and managing iodinated contrast media hypersensitivity. Allergy. 2021 May;76(5):1325-1339. doi: 10.1111/all.14656. PMID: 33170954.

Free Access

Skin testing in patients with hypersensitivity reactions to iodinated contrast media – a European multicenter study

K. Brockow, A. Romano, W. Aberer, A. J. Bircher, A. Barbaud, P. Bonadonna, E. Faria, G. Kanny, M. Lerch, W. J. Pichler, J. Ring, J. Rodrigues Cernadas, E. Tomaz, P. Demoly, C. Christiansen ... See all authors

First published: 21 January 2009 | https://doi.org/10.1111/j.1398-9995.2008.01832.x | Citations: 242

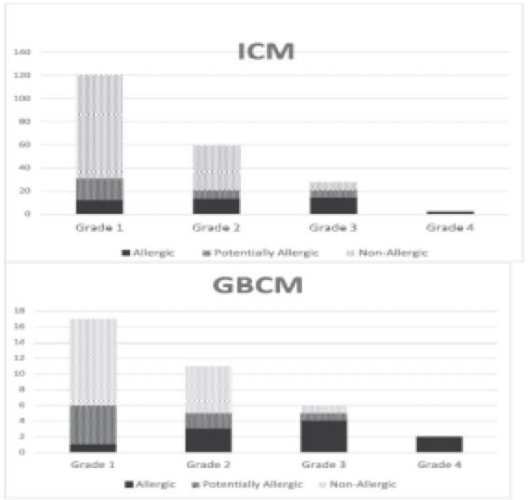
DELAYED SKIN TESTS WERE POSITIVE IN 37 OF 98 NONIMMEDIATE REACTORS.
NINE PATIENTS WERE DELAYED IDT POSITIVE BUT PT NEGATIVE, WHILE SEVEN PATIENTS WERE DELAYED IDT NEGATIVE BUT PT POSITIVE.

EClinicalMedicine
Published by THE LANCET

Immediate Hypersensitivity to Contrast Agents: The French 5-year CIRTACI Study

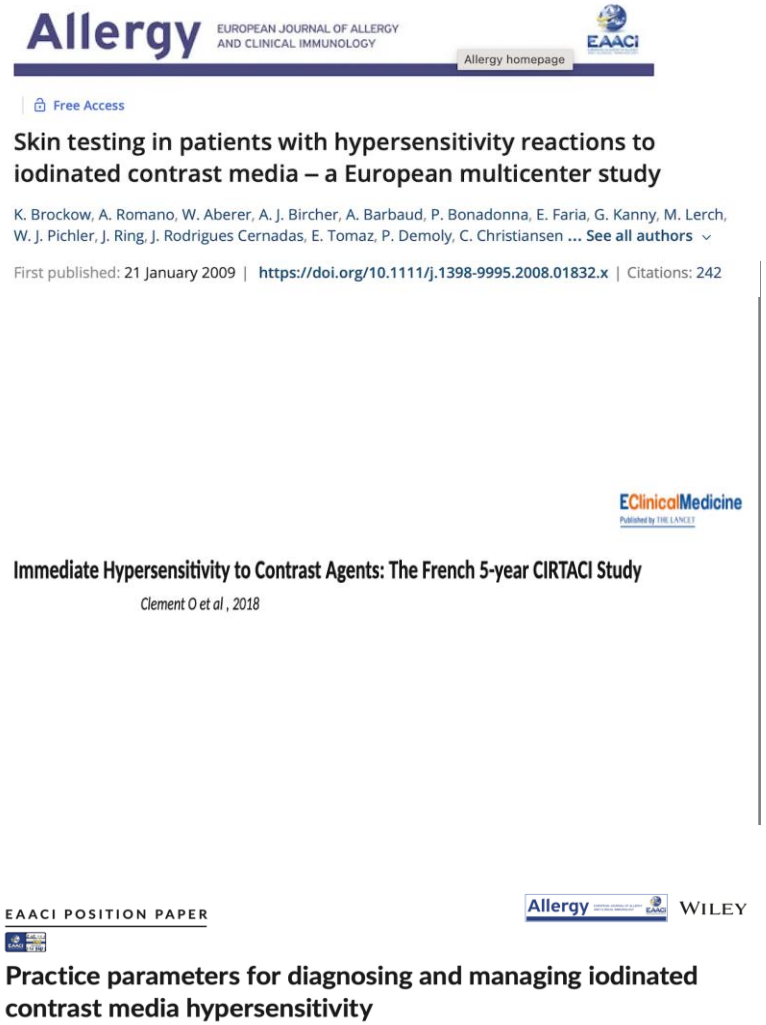
Clement O et al , 2018

Allergic IH was diagnosed by intradermal tests (IDT)with the culprit CM diluted 1:10, “potentially allergic” IH by positive IDT with pure CM, and non-allergic IH by negative IDT.



Among 245 skin-tested patients (ICM=209; GBCM=36), **allergic IH to ICM**, was identified in 41 **(19.6%)** and to **GBCM** in 10 **(27.8%).** Skin cross-reactivity was observed in 11 patients with **ICM (26.8%)** and 5 with **GBCM (50%).** **Non-allergic IH** was observed in 152 patients **(62%)** (ICM:134; GBCM:18). **Potentially allergic IH** was diagnosed in 42 patients **(17.1%)** (ICM:34; GBCM:8). The delay, severity grade,and mediator release were intermediate between the two other groups.

Skin testing with pure contrast agent, as it is more sensitive than the usual 1:10 dilution criteria



IF THE TIME INTERVAL BETWEEN THE REACTION AND THE STUDY IS WITHIN 2-6 MONTHS, 50% OF PATIENTS TESTED SHOW POSITIVE RESULTS, DECREASING TO UP 18% FOR PATIENTS TESTED AT OTHER TIME POINTS (EARLIER THAN 2 MONTHS OR LATER THAN 6 MONTHS).

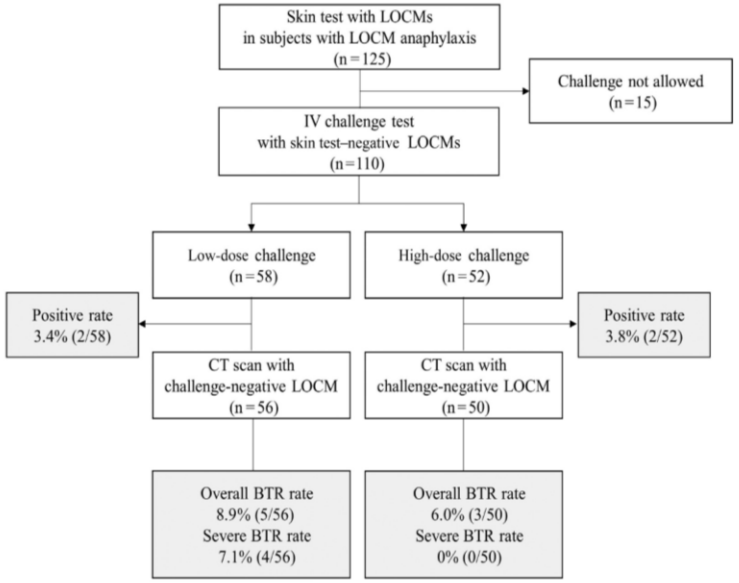
A RECENT MULTICENTER PROSPECTIVE STUDY DOCUMENTED ALLERGY IN ONE IN TENTH, A QUARTER, HALF AND ALL PATIENTS WITH CUTANEOUS, MODERATE-SYSTEMIC, LIFE-THREATENING ANAPHYLAXIS, AND CARDIAC ARREST, RESPECTIVELY.

NEGATIVE PREDICTIVE VALUE (NPV) OF ST WITH ICM HAS BEEN REPORTED TO BE 80-97%

Original Article

Validation of Practical Pathway in Patients With Anaphylaxis to Low Osmolar Contrast Media: A Retrospective Cohort Study

Kyung-Min Ahn, MD[a,b], Yoon Hae Ahn, MD[a], Min Kyoung Cho, MD[c], Dong Yoon Kang, MD, PhD[c], Suh Young Lee, MD, PhD[a,b], and Hye-Ryun Kang, MD, PhD[a,b,c] *Seoul, Korea*



75% POSITIVI AD ALMENO UN MDC

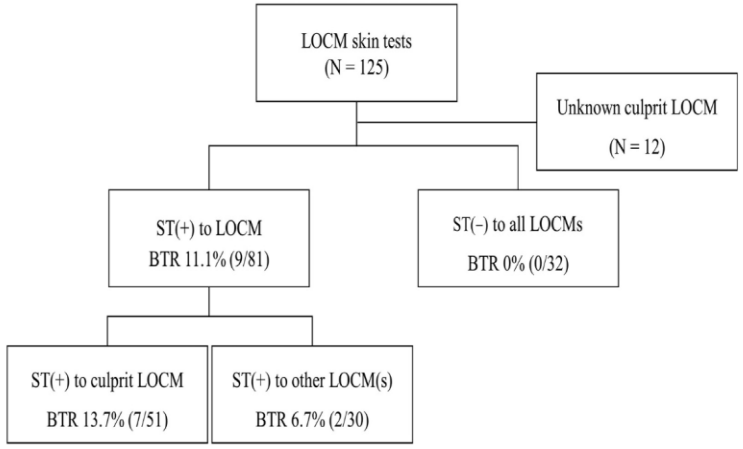


FIGURE 3. The comparison of BTR rates in cases according to the result of skin testing. *ST*, Skin test.

THE CHALLENGE TEST WAS PERFORMED AT 15-MINUTE INTERVALS USING 2 DIFFERENT PROTOCOLS: LOW- DOSE (2 ML, 5 ML, AND 10 ML) AND HIGH-DOSE (5 ML, 30 ML) PROTOCOLS.

PATIENTS RECEIVED CT SCANS OR ANGIOGRAPHY WITH CHALLENGE- NEGATIVE LOCMS AFTER PRETREATMENT WITH 4 MG OF INTRAVENOUS CHLORPHENIRAMINE AND 40 MG OF METHYLPREDNISOLONE 1 HOUR BEFORE REEXPOSURE.

Immediate hypersensitivity reactions to iodinated contrast media: The diagnosis of allergy by skin testing

Among 74 patients with an immediate hypersensitivity reaction (IHR) to iodinated contrast media (ICM), the rate of allergic patients confirmed by positive prick test or diluted intradermal test (IDT) was 8.1%. 12.5% of re-exposed patients had a recurrent IHR despite negative skin tests. Investigations on pure IDT to ICM and development of drug provocation test may provide additional safety nets to uncover recurrent ICM reactors. Agreements among allergists are needed to unify practices.

TABLE 2 Re-exposure to ICM: 5 patients out of 40 with a recurrent IHR to ICM after the allergy work-up

Sex	Age at skin tests (years)	ICM (administration route)	Grade of initial reaction	Time from initial reaction to skin tests (months)	Skin tests	Year of skin tests	ICM reintroduced (route of administration)	Grade
Male	66	Unknown (IA)	II	60	Negative	2016	Iohexol (IA)	II
Female	51	Ioversol (IV)	III	6	Positive IDT Iodixanol Iohexol Ioversol	2017	Iopamidol (IV)	II
Male	72	Ioversol (IV)	II	5	Negative	2017	Iohexol (IV)	II
Female	69	Iodixanol (IV)	III	11	Negative	2018	Iodixanol (IV)	IV
Male	58	Iodixanol (IV)	I	72	Negative	2018	Iohexol (IV)	I

Abbreviations: IA, intra-articular; IDR, intradermal reaction; IV, intravenous.

Five re-exposed patients (12.5%) had a recurrent IHR after a new ICM administration despite negative ST for the ICM agent (Table 2). The NPV of the allergy work-up for predicting an IHR to ICM was 88.1% [95% CI 74.4; 96]. Five IHR among 42 re-exposures were observed. Four out of these five IHR were less or equally severe

Original Article

Radiocontrast Media Hypersensitivity: Skin Testing Differentiates Allergy From Nonallergic Reactions and Identifies a Safe Alternative as Proven by Intravenous Provocation

Axel Trautmann, MD[a], Knut Brockow, MD[b], Valeria Behle, MD[a], and Johanna Stoevesandt, MD[a] *Würzburg and Munich, Germany*

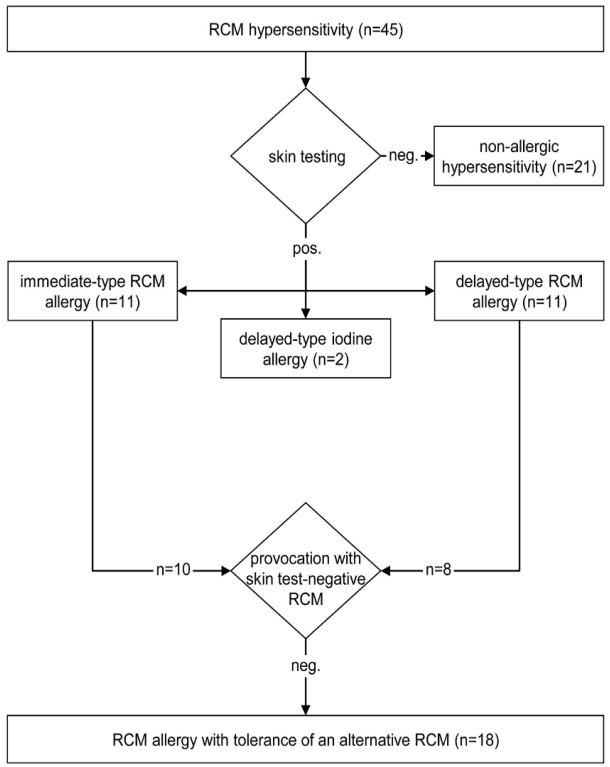


TABLE II. Patient cohort

Clinical parameters	Nonallergic (not IgE-mediated) hypersensitivity (n = 21)	Immediate-type (IgE-mediated) allergy (n = 11)	Delayed-type (T- cell—mediated) allergy (n = 13)
Males/females	5/16	4/7	6/7
Age (y), median (range)	55 (20-79)	61 (46-77)	58 (44-80)
Radiological examination			
Coronary angiography	3	6	5
Computed tomography	7	2	5
Urography	10	3	2
Phlebography	1	0	1
Incriminated RCM			
Iopamidol	0	1	1
Iopromide	7	4	0
Iomeprol	10	6	9
Iobitridol	4	0	1
Iohexol	0	0	1
Iodixanol	0	0	1
Latency time from RCM administration to first symptoms			
<1 min	4	1	NA
1-5 min	10	10	NA
6-15 min	7	0	NA
6-12 h	NA	NA	4
1-2 d	NA	NA	7
3 d	NA	NA	2
Clinical signs			
Delayed skin reaction			
Maculopapular exanthem	NA	NA	11
Systemic hypersensitivity (DRESS)	NA	NA	1
Fixed drug eruption	NA	NA	1
Anaphylaxis			
Mild	20	0	NA
Moderate	1	6	NA
Severe	0	5	NA
Time interval between RCM-induced reaction and allergy testing			
<6 mo	5	8	10
6-12 mo	10	2	2
>1-5 y	6	1	1

NA, not applicable.

Is there a role for Drug Provocation Test?

- EITHER RE-EXPOSITION OR DPT CAN BE PERFORMED TO CONFIRM TOLERANCE TO A SKIN TEST-NEGATIVE ICM; THE DECISION IS BASED ON AVAILABILITY OF DPT AND RISK-BENEFIT ANALYSIS (STRONG/HIGH).
- DPT WITH ICM CAN BE DONE AS A DIAGNOSTIC TEST EITHER WITH THE CULPRIT OR WITH AN ALTERNATIVE ICM (STRONG/HIGH).
- AVAILABLE PROTOCOLS SHOULD BE STANDARDIZED AND VALIDATED (STRONG/HIGH).
- RENAL FUNCTION NEEDS TO BE CAREFULLY MONITORED (STRONG/HIGH).
- AS IN ANY DPT, THE DECISION NEEDS TO BE TAKEN BASED ON A RISK-BENEFIT ANALYSIS OF EACH PATIENT AND SHOULD BE DONE ONLY IN WELL-EQUIPPED CENTERS AND BY TRAINED PERSONNEL IN IMMEDIATE EMERGENCY TREATMENT (STRONG/LOW).
- THE POSSIBILITY TO PERFORM THE DPT TOGETHER WITH THE RADIOLOGICAL EXAMINATION SHOULD BE CONSIDERED (STRONG/LOW).
- DPT IS NOT INDICATED IN PATIENTS AT RISK (RENAL COMPLAINTS, HYPERTHYROIDISM, RADIOACTIVE IODINE THERAPY, PREGNANT AND BREASTFEEDING WOMEN, NEPHROTOXIC MEDICATION, ETC) (STRONG/HIGH).

Torres MJ et all. Practice parameters for diagnosing and managing iodinated contrast media hypersensitivity. Allergy. 2021 May;76(5):1325-1339. doi: 10.1111/all.14656. PMID: 33170954.

Circulation

PERSPECTIVE

Contrast-Induced Acute Kidney Injury and Cardiovascular Imaging: Danger or Distraction?

Matthew S. Davenport, MD; Mark A. Perazella, MD; Brahmajee K. Nallamothu, MD

Use of Intravenous Iodinated Contrast Media in Patients with Kidney Disease: Consensus Statements from the American College of Radiology and the National Kidney Foundation

Matthew S. Davenport, Mark A. Perazella, Jerry Yee, Jonathan R. Dillman, Derek Fine, Robert J. McDonald, Roger A. Rodby, Carolyn L. Wang, Jeffrey C. Weinreb

EAACI POSITION PAPER

Allergy WILEY

Practice parameters for diagnosing and managing iodinated contrast media hypersensitivity

PREVALENZA È STATA SOVRASTIMATA PER ASSENZA DI GRUPPI DI CONTROLLO NEGLI STUDI E NON ESCLUSIONE DI ALTRE CAUSE (CONTRAST-INDUCED AKI VS CONTRAST-ASSOCIATED AKI)

A RISCHIO SOGGETTI CON CC < 45 ML/MIN/1.73 M

FATTORI DI RISCHIO:
-DIABETE
-IPOALBUMINEMIA
-ANEMIA
-IPOVOLEMIA/ISTABILITÀ EMODINAMICA
-DOSE DI MDC NELLE PROCEDURE ANGIOGRAFIE
-TIPO MDC (IPEROSMOLARI E IOEXOLO>IODIXANOLO)

NEI PAZIENTE A RISCHIO:
-IDRATAZIONE CON SOLUZIONI ISOTONICHE
-SOSPENDERE METFORMINA 24 ORE PRIMA

RESEARCH LETTER

Adverse reactions to iodinated contrast media: Safety of a study protocol that includes fast full-dose parenteral challenge tests searching for an alternative contrast media

Francisco Vega, Maria Victoria Múgica, Raphaëlle Bazire, Laura Argíz, Maria Teresa Belver, Alfonsa Friera, Carlos Blanco

First published: 21 October 2019 | https://doi.org/10.1111/cea.13518 | Citations: 6

TABLE 1 Challenge tests in previous studies: ICM dose, administration rate and total time

HSR type	References	Increasing intravenous doses	Interval between doses	Full dose	Total time	Number of Days
Immediate HSR	Trcka. 2008	0.05-0.5-1-5-7.5-10-25 cc	30 min	49.05 cc	120 min	1
	Salas. 2013	5-15-30-50 cc	45 min	100 cc	180 min	1
	Sesé. 2016	10 cc	One dose	10 cc	Not reported	1
	Morales-Cabeza 2017	5-30-60 cc on day 1 120 mL on day 2	30 min	95 cc on day 1 120 cc on day 2	60 min	2
	Trautmann 2019	0.05- 0.5-1-5-7.5-10-25 cc	30 min	49.05 cc	3 h	1
Delayed HSR	Vernassiere 2004	1/100 cc of full dose on day 1 1/10 cc of full dose on day 2	24 h	1/100 cc on day 1 1/10 cc on day 2	One dose/day	2
	Seitz 2009	1-5-7.5-10-30 cc	1 h	53.5 cc	4 h	1
	Torres. 2012	5-10-15 cc on day 1 20-30-50 cc on day 2	1 h	100 cc	2 h on day 1 2 h on day 2	2 (1-wk interval)
	Gracia-Bara 2019	5-20 cc on day 1 50-50 cc on day 2	1 h	25 cc on day 1 100 cc on day 2	2 d	2 (1-wk interval)
	Trautmann 2019	1-5-7.5-10-25 cc	30 min	48.5 cc	2 h	1
Immediate and delayed HSR	Lerondeau 2016	1/100 + 1/10 cc of full dose	1 h	1.1/100 cc of full dose	1 h	1
	Soria. 2019	5-15-30 cc	2 h	50 cc	4 h	1
	Our protocol	100 cc	Single dose	100 cc	12 min	1

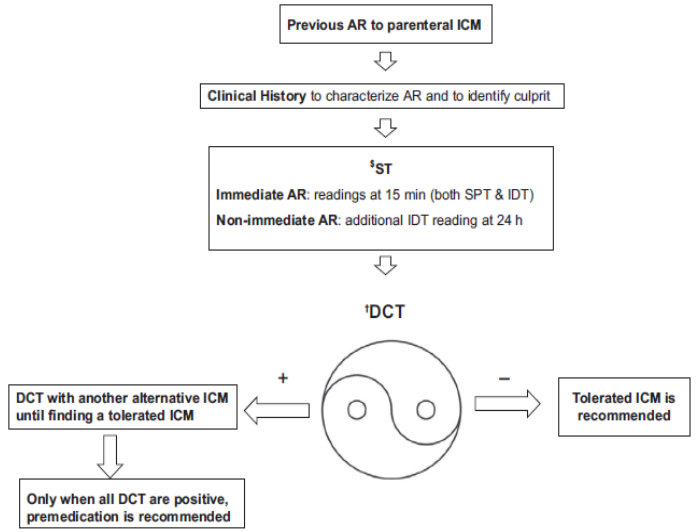


FIGURE 1 Algorithm to identify an alternative iodinated contrast media in possible allergic patients. $ST (skin tests): Immediate readings were considered positive when a mean weal diameter of ≥3 mm in skin prick tests (SPTs), or an increase in the initial mean weal diameter of at least 3 mm surrounded by erythema in intradermal tests (IDT), was observed. Delayed IDT readings were positive if an erythematous induration occurred in the ST site at 24 h. †DCT (drug challenge test): 100 cc of alternative ICM (avoiding involved and/or positive skin-tested ICM), administered in 12 min; time interval between challenge tests ≥7 d. AR, adverse reaction; ICM, iodinated contrast media

NPV 66-92%

Gadolinium-based contrast agents (GBCAs)

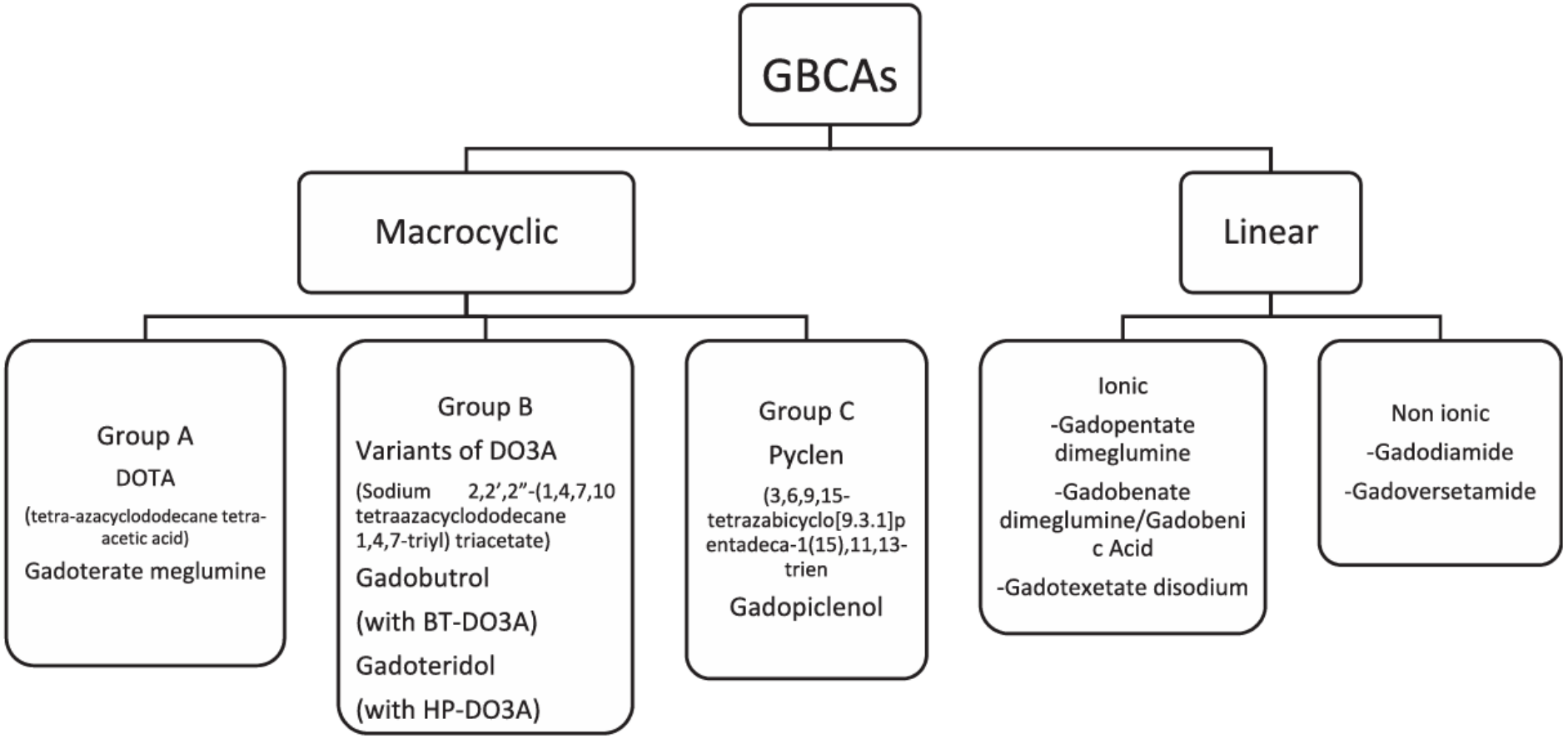


FIGURE 1 | Classification of GBCAs based on strucutural class (macrocyclic vs. linear); each class is further subdivided according to ionicity (ionic vs. non-ionic) and chemical structure of chelating agents (group A, B and C) (adapted from Gracia Bara et al. [1] and Vega et al. [14]).

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THE ADVERSE EVENTS (AES) FREQUENCY IS LOW AND RANGES FROM **0.04% TO 2.4%**, WITH A TRUE PREVALENCE PROBABLY CLOSE TO **0.1%**, EVEN RARER IN CHILDREN

MOST AES ARE PREDICTABLE REACTIONS (**TYPE A**), PROBABLY CAUSED BY INCREASED CELL OSMOLARITY AND SUBSEQUENT DAMAGE

HYPERSENSITIVITY REACTIONS (**TYPE B**) ARE LESS COMMON, OCCURRING FROM **0.004% TO 0.7%**.

IMMEDIATE HSRS (IHSRS) REPRESENT THE MAJORITY OF HSRS (75% 100%); ANAPHYLAXIS COUNTS FOR 0.01%, WITH A DEATH RATE OF ABOUT 0.0019%.

NON-IMMEDIATE HSRS (**NIHSRS**) HAVE AN INCIDENCE OF **0.05%** AND OCCUR ON THE SAME ADMINISTRATION DAY IN ABOUT HALF OF THE CASES

Table 2. Risk factors for developing GBCA-IHRs

Risk factors		Refs.
Sex	Women	Aran *et al.* [9] Jung *et al.*[6] Prince *et al.*[64] JR. Dillman *et al.* [57]
Net charge in solution	Ionic	Behzadi *et al.*[10]
Structure of GBCA	Macrocyclic	Behzadi *et al.*[10]
Previous reaction to GBCA	Yes	Lukawska *et al.*[12] Nelson *et al.*[11]
Atopy	Reaction to ICM	Lukawska *et al.*[12] Murphy *et al.*[8] RB. Lufkin *et al.*[13]
Exploration	Abdomen-pelvis, liver and thoracic	Aran *et al.*[9]
Setting	Outpatient and emergency	Aran *et al.*[9]
Protein binding	Yes	Behzadi *et al.* [10] Runge *et al.*[65]

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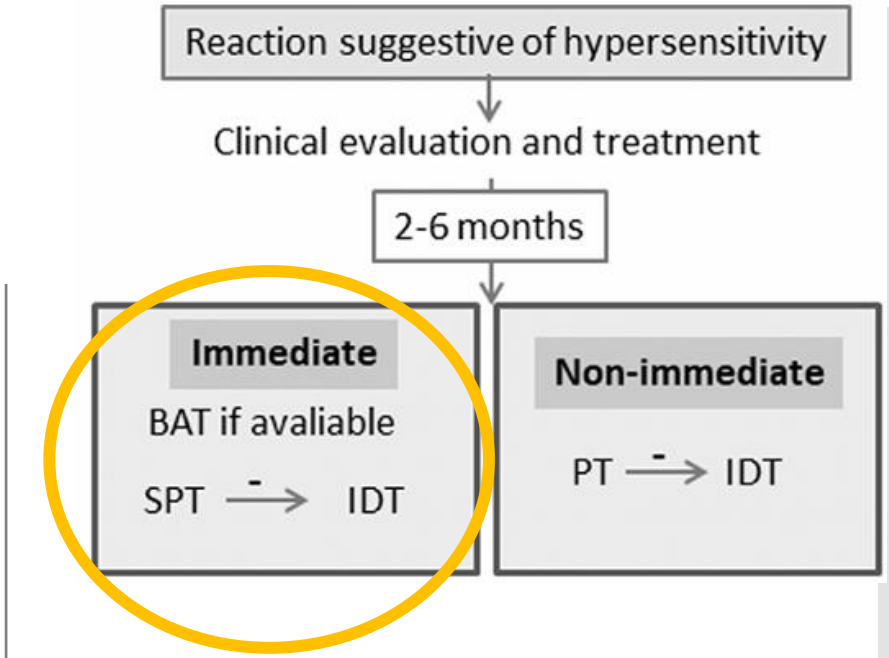
confirmed GBCA-HSRs have been carried out. Skin tests have been usually performed following the EAACI-ENDA recommendations [39]. Skin prick testing with undiluted GBCA and, if negative, intradermal testing with a 1 : 1000, 1 : 100 and 1 : 10 dilutions are recommended [7,14,20▪,22–25,33,40–46], intradermal testing with undiluted GBCA preparations may induce false-positive results [23]. Skin testing should be performed with the GBCA involved in the initial reaction if known, and a panel of several GBCAs of different molecular structure to explore further alternative agents [16,40,45].

The percentage of skin testing positivity may range between 15.45 and 57.6% of cases experiencing immediate reactions [7,24,32▪,33,40,44]. Although positive skin prick test with GBCAs has been reported [22,23,26,33,40,41,44,46,47], most cases (up to 80%) with positive skin tests had positive intradermal tests (IDTs) [33]. In immediate reactions, skin test positivity increased with reaction severity [32▪,33].



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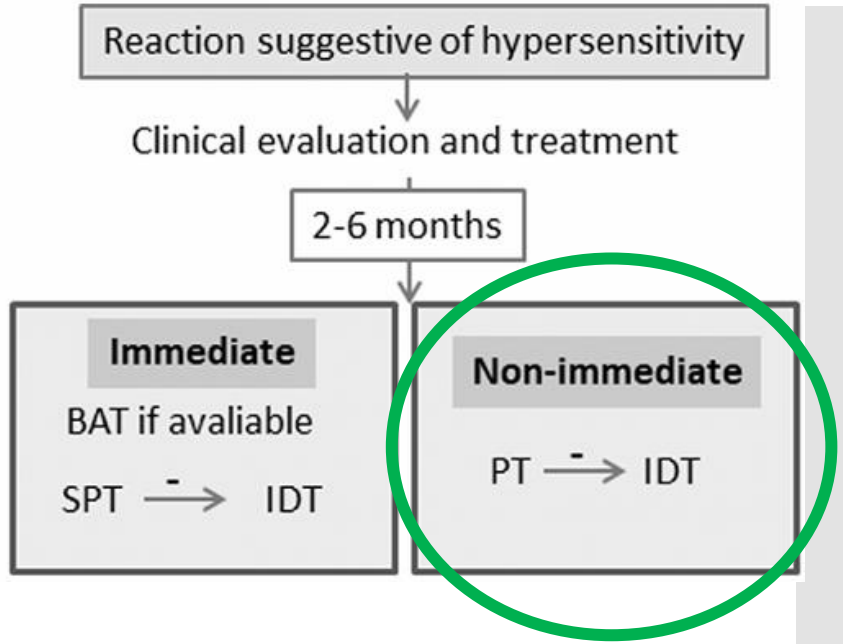
Regarding NIRs, patch tests with undiluted GBCAs are recommended, and if negative IDTs at a 1 : 10 dilution. Positive skin tests reported in NIRs are scarce [34,36]. If IDT resulted negative at the 1 : 10 dilution, some authors performed IDTs with the undiluted GBCAs finding delayed positive response [31].



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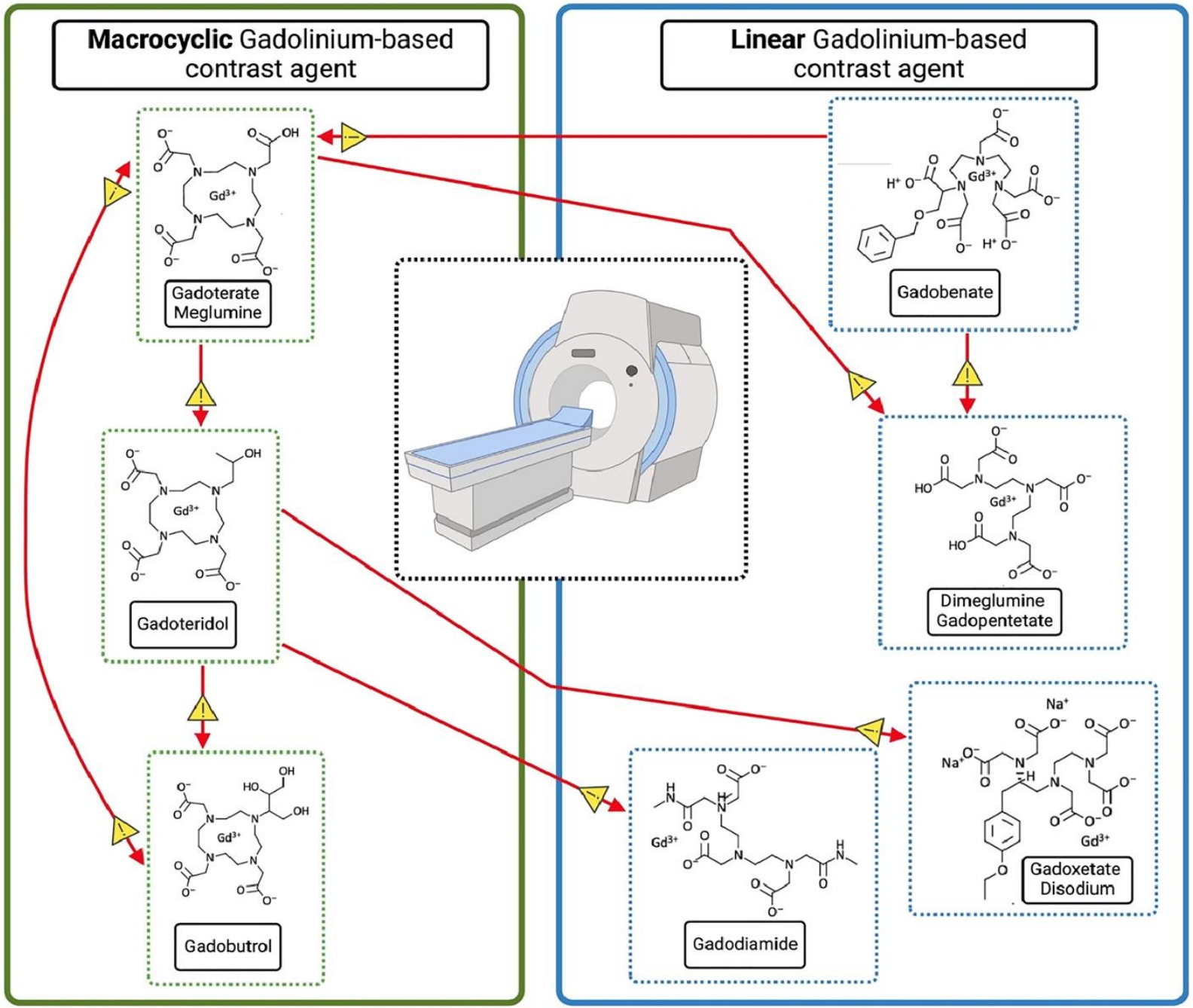

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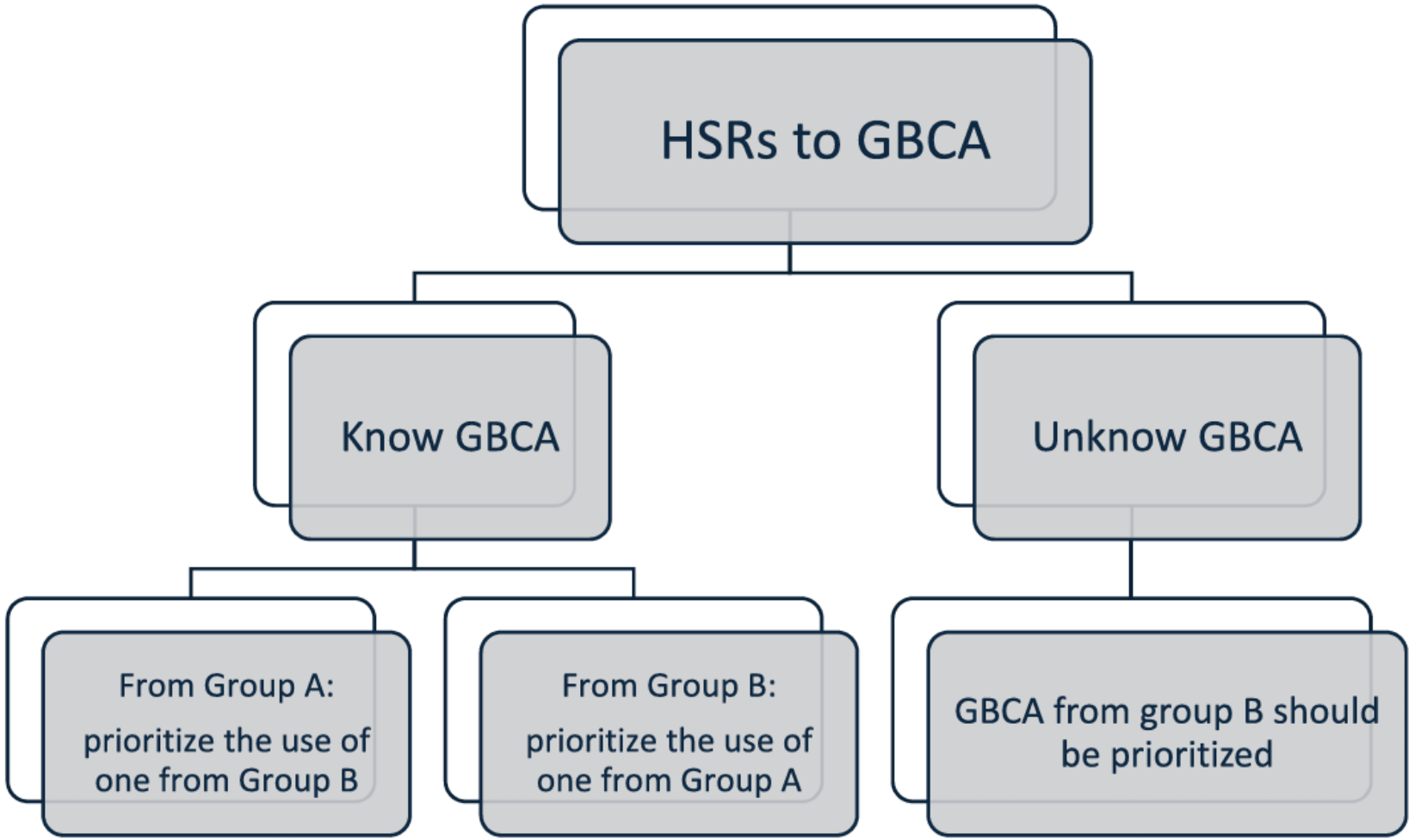
Gadolinium-based contrast agents (GBCAs)



FIGURE

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FIGURE 3 | The empirical selection of an alternative GBCA in case of previous HRs (adapted from Vega et al. [14]).

Anaphylaxis to trometamol excipient in gadolinium-based contrast agents for clinical imaging

Joanna Lukawska, MBBS[a], Deepal Mandaliya, MRPharmS[b], A.W. Edith Chan, PhD[c], Amy Foggitt, BSc[a], Therese Bidder, BSc[a], Jennifer Harvey, BSc[a], Lisa Stycharczuk, DCR(R)[a], and Sotirios Bisdas, MD[a,c]

Trometamol/Tromethamine (C4H11NO3), an organic amine, is used extensively as an excipient in buffer solutions in various topical as well as enteral and parenteral products. It can also be used on its own as a buffer for the treatment of severe metabolic acidosis. In the cosmetic industry, it is used as an emulsifying agent for creams and lotions. It is not clear when and how our patient became sensitized to trometamol. However, because the substance is commonly used in adhesives, coating products, fillers, putties, plasters, inks and toners, leather treatment products, lubricants, polishes, textile treatment products and dyes, as well as perfumes and fragrances, it would be very difficult to establish this. Importantly, trometamol is contained in many enteral and parenteral medications such as co-trimoxazole for infusion, Hemabate, Humalog, Keral, Menitorix, midazolam, oxaliplatin, Skudexa, and temazepam. Patients

TABLE 1 | State of art of DPTs in GBCAs HSRs.

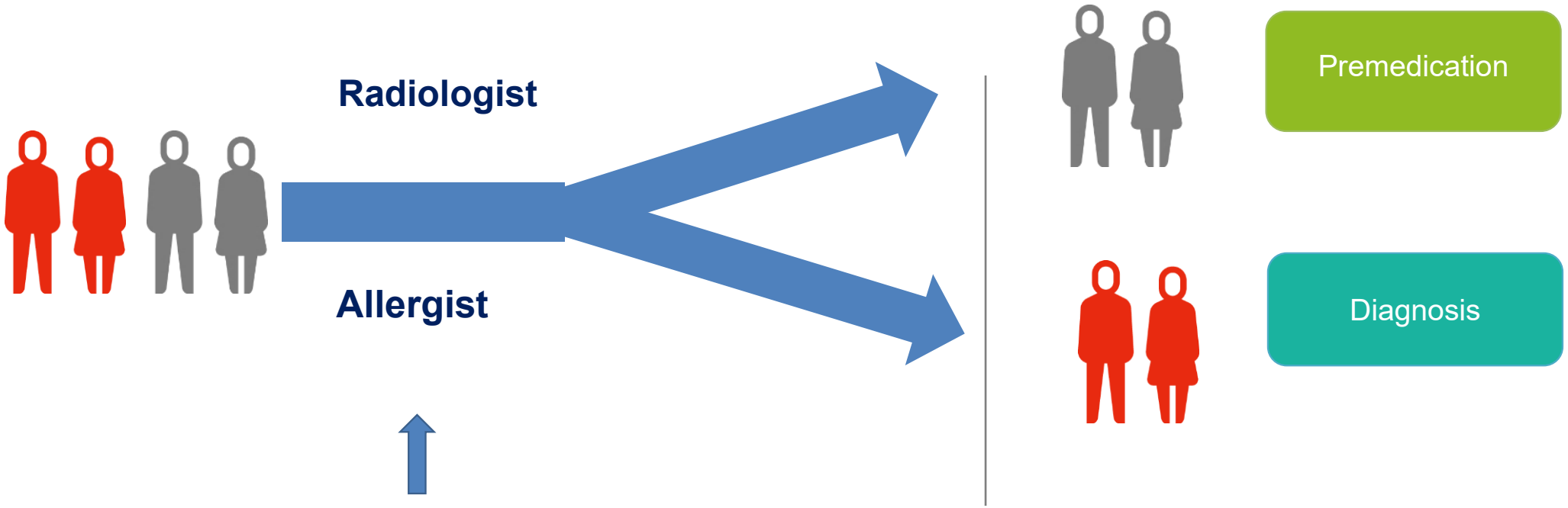
Study	Patients	Timing of reaction	Positive ST	Tolerated GBCAs	Non tolerated GBCAs	Protocols
Moulin et al. [47]	1	IHR	Gadoterate meglumine	Gadobenate dimeglumine	—	Unspecified/re-exposed
Chiriac et al. [48]	27	IHR	Gadobenate dimeglumine (in 1 patient)	Gadopentetate dimeglumine Gadobenate dimeglumine Gadoterate meglumine Gadoteridol	—	Unspecified/re-exposed
Kolenda et al. [41]	33	IHR	Gadobenate dimeglumine Gadoterate meglumine Gadobutrol (in 19 patients, 57%)	Gadobenate dimeglumine Gadoterate meglumine Gadobutrol	—	Unspecified/re-exposed
Moreno-Escobosa et al. [45]	1	IHR	Gadobenate dimeglumine Gadodiamide Gadoterate meglumine	—	Gadoteridol	Unspecified/re-exposed
Seta et al. [36]	14	IHR and NIHR	Gadobutrol Gadoteridol Gadoterate meglumine (all positive) NPV 86%	Gadoterate meglumine Gadopentetatedimeglumine	Gadoterate meglumine Gadoteric acid	Single-blind placebo-controlled DPT, during 8-hours hospital stay with 1 mL of the GBCA (1/10 of usually injected dose for MRI)
Hojreh et al. [49]	17	IHR	—	Gadobenate dimeglumine Gadoterate meglumine Gadobutrol	—	Unspecified/re-exposed
Mankouri et al. [38]	132	IHR and NIHR	Gadobenate dimeglumine gadoterate meglumine gadobutrol gadoteridol (in 18 patients, 13,6%)	Gadodiamide Gadoterate meglumine Gadobutrol	—	Unspecified/re-exposed
Gallardo et al. [50]	5	IHR	Gadoterate meglumine Gadobutrol (in 2 patients)	Gadoxetate disodium Gadoterate meglumine	Gadobutrol	Unspecified/re-exposed
Vega et al. [34]	16	INH and NIHR	Gadobutrol (in 1 patient)	Gadoteric acid (0.2 mg/kg)	Gadoteric acid Gadobutrol (0.1 mg/kg)	1/3 dose at a rate of 120 cc/h and, immediately after, the remaining 2/3 at 40 cc/h; total infusional time 8′
Stehlin et al. [35]	9	IHR	Gadobenate Gadobutrol gadoteridol (in 3 patients)	Gadobenate Gadobutrol gadoteridol	Gadobenate	2-Step, placebo-controlled DPT, 1 mL IV (1/5 dose), if negative after 20-30′ 4 mL IV, then evaluation after 60′
Macias et al. [26]	1	NIHR	Gadoxetate disodium	—	Gadoteric acid	

TABLE 1 | (Continued)

Study	Patients	Timing of reaction	Positive ST	Tolerated GBCAs	Non tolerated GBCAs	Protocols
Rodriguez-Nava et al. [36]	1	IHR	Gadobenate dimeglumine gadoterate meglumine	—	Gadobutrol	10% dose; monitor for 30 min followed by rest of the dose and monitored for 1 h
Gallardo et al. [51]	1	NIHR	—	Gadoxetate disodium (1st day 453.58 mg, 2nd day 1360.73 mg)	Gadobutrol (1st day 1209.44 mg, 2nd day 4535.4 mg)	2-day, with 1 week of delay

Note: We highlighted, when available, the positivity of skin tests, the tolerated GBCAs, and the protocols for DPTs. Unfortunately, the lack of data on sensitivity, specificity, and predictive values is a major limitation of the papers taken into account, which were mostly case reports and case series.

ONE SIZE FITS ALL



ONE SIZE DOES NOT FIT ALL

Examples of premedication protocols

Study	Type of Study	Pre-medication scheme
Lee et al.	Retrospective Cohort Study	For patients with a mild index reaction: 4 mg of intravenous (IV) chlorpheniramine 30 minutes before ICM administration; For patients with a moderate index reaction: 40 mg of intravenousmethylprednisolone and 4 mg of IV chlorpheniramine 1 hour before ICM administration; For patients with a severe index reaction: 40 mg of IV methylprednisolone 4 hours and 1 hour before and 4 mg of IV chlorpheniramine 1 hour before ICM administration via the IV catheter inserted for ICM injection.
Park et al.	Retrospective Cohort Study	Not predefinite pre-medication regimen, but decided by physician in charge; histamines and steroids administered 0.5–1 hour beforere-exposure to ICM
Mervak et al.	Retrospective Cohort Study	50 mg prednisone administered 13 and 7 hours and 1 hour before CT (total, 150 mg prednisone) and 50 mg diphenhydra mine administered 1 hour before CT
Jung et al.	Retrospective Cohort Study	Not predefinite pre-medication regimen, but decided by physician in charge; histamines and steroids (usually 40 mg of methylprednisolone IV and 4 mg of chlorpheniramine and/or 20 mg of famotidine) administered 0.5–1 hour beforere exposure to ICM

Examples of premedication protocols

Study	Type of Study	Pre-medication scheme
Kolbe et al.	Retrospective Cohort Study	Diphenhydramine alone (25–50 mg orally or intravenously 1 h prior to imaging) Corticosteroid alone (two doses of methylprednisolone 32 mgorally administered 12 and 2 h prior to imaging) Combined corticosteroid plus diphenhydramine
Jha et al.	Retrospective Cohort Study	IV corticosteroid (methylprednisone 125 mg, hydrocortisone 100 mg or dexamethasone 16 mg), IV H2-blocker (famotidine 50 mg), and IV antihistamine (diphenhydramine 25 mg)
Bae Y et al	Retrospective Cohort Study	In case of mild reaction: chlorpheniramine 4 mg alone IV or intramuscularly 1 hour before ICM In case of severe reactions: IV hydrocortisone 200 mg plus chlorpheniramine 4 mg 1 hour before ICM.

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THE SEVERITY-BASED STRATIFIED PROPHYLAXIS REGIMENS REDUCED THE RISK OF BREAKTHROUGH REACTIONS IN PATIENTS WITH A HISTORY OF HSR TO ICM; ANTIHISTAMINE ONLY FOR MILD INDEX HSRS, A COMBINATION OF ANTIHISTAMINE AND SINGLE-DOSE CORTICOSTEROID (METHYLPREDNISOLONE 40 MG) FOR MODERATE INDEX HSRS, AND A COMBINATION OF ANTIHISTAMINE AND MULTIPLE-DOSE CORTICOSTEROID (METHYLPREDNISOLONE 40 MG) FOR SEVERE INDEX HSRS

PREMEDICATION CANNOT COMPLETELY PREVENT THE RECURRENCE OF AN IMMEDIATE HSR, ESPECIALLY SEVERE HSRS SUCH AS ANAPHYLAXIS

THE USEFULNESS OF PREMEDICATION FOR DELAYED HSR IS STILL LACKING

STANDARD PREMEDICATION PROTOCOLS DETAILING DRUG CHOICE, DOSAGE, AND INTERVAL AND FREQUENCY OF ADMINISTRATION BEFORE ICM REEXPOSURE HAVE NOT BEEN PROPERLY ESTABLISHED

GRAZIE A TUTTI