



# Diagnosing and Managing Patients with Reactions to Radiocontrast Media

Knut Brockow, MD 

## Address

Department of Dermatology and Allergy Biederstein, School of Medicine, Technical University of Munich, Biedersteiner Strasse 29, 80802, Munich, Germany  
Email: knut.brockow@tum.de

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## Abstract

*Purpose of the review* Iodinated radio contrast media (RCM) belong to the most common elicitors of drug hypersensitivity reactions (HR). Urticaria or anaphylaxis may occur  $\leq 1(-6)$  hour(s) (immediate HR) and exanthems (non-immediate HR) develop  $> 6$  h after application of RCM. Evidence for an immunologic mechanism of RCM HR against the different RCM benzene ring molecules and the benefit of allergological testing in patients with previous hypersensitivity reactions is progressively increasing.

*Recent findings* Positive skin tests can confirm allergy in patients with previous reactions to RCM and help to select alternative better tolerated RCMs. Severe hypersensitivity reactions are mainly caused by an allergic mechanism, whereas the majority of non-severe reactions appear to be non-allergic. Skin testing is highly recommended to help identify allergic hypersensitivity reactions and to select alternatives. Using structurally different RCM is more effective than premedication for the prevention of future reactions. Drug provocation tests to RCM have been increasingly used, but are not yet standardized among different centers.

*Summary* In patients with previous severe hypersensitivity reactions to RCM, skin testing is recommended. For future RCM-enhanced examinations in patients with previous reactions, structurally different, skin test-negative preparations should be applied. Drug provocation tests do confirm or exclude RCM hypersensitivity or may demonstrate tolerability of alternative RCMs.

## Introduction

Modern medicine increasingly relies on examinations with radio contrast media (RCM) for diagnostic purposes, whereas these are normally well tolerated. However, because of more than 70 million applications of RCM administered worldwide per year, adverse reactions are not uncommon after their use [1]. A part of the reported reactions are predictable toxic reactions, such as nephrotoxicity, neurotoxicity, vasovagal reactions, transient warmth/flushing, metallic taste, pallor, weakness, nausea, and vomiting as well as bradycardia. Another part is even

causally unrelated to exposure to RCM, e.g., stress-induced (spontaneous) acute urticaria, exanthems elicited by other drugs given at the same time, or unspecific subjective symptoms often associated with anxiety. However, thirdly, allergic and non-allergic hypersensitivity reactions do occur and present either only with cutaneous reactions (urticaria, pruritus, angioedema, exanthem) or with systemic manifestations including anaphylaxis [2•]. This article focusses on recent advances in our understanding of hypersensitivity reactions to RCM.

## Chronological classification of radiocontrast media reactions

RCM hypersensitivity reactions may occur either immediately within 1 (in very exceptional cases history of up to six) hour(s) after RCM administration (immediate hypersensitivity reactions, IHR) or non-immediate hypersensitivity reactions (NIHR) developing > 6 h, mostly 1–3 days and up to 10 days after RCM application [3, 4]. Almost all IHR start within 1 h, most severe reactions (96%) within 20 min and the majority of IHRs to RCM occur even within the first 5 min after RCM administration [5]. In IHRs, symptoms resemble manifestations also seen in anaphylaxis ranging from isolated skin involvement to full anaphylaxis involving more than one organ system and in NIHRs present with exanthems, mostly maculopapular exanthems [6].

## Risk factors for radiocontrast media reactions

Reported incidences of hypersensitivity reactions to RCM vary widely because of different definitions of anaphylaxis, IHR, NIHR, and RCM attributed to toxicity, use of premedication. Mild IHR to nowadays non-ionic (low osmolar) RCM are estimated to occur in 0.5–2.0% administrations and severe reactions in 0.02–0.04% [5]. The incidence of NIHR to RCM remains unclear, but skin reactions may be around 0.5 to 3%; with possibly a higher incidence for the dimeric isoosmolar RCM iodixanol [7, 8]. Whereas several other minor factors have been discussed in individual studies, the only well-proven major risk factor for IHR as well as for NIHR is re-exposure after previous reaction to RCM. Interestingly, a previous IHR is no risk factor for an NIHR and vice versa. IHRs to RCM are substantially less often reported for intra-arterial and for extravascular (e.g., gastrointestinal, genitourinary) administrations [9, 10].

## Clinical manifestations

Manifestations of IHR to RCM range from mild skin symptoms, such as urticaria, to anaphylaxis [11, 12•, 13•]. Fatal anaphylaxis does occur with an estimated fatality rate of approximately 1 to 2 per 100,000 procedures [14–16].

Most IHR present with cutaneous symptoms, such as urticaria/angioedema and pruritus [11]. Anaphylaxis affects mostly the skin together with an involvement of other organ systems, e.g., bronchospasm and wheezing, additional nausea and vomiting, or tachycardia and hypotension resulting in anaphylactic shock. An acute coronary syndrome caused by reduced blood flow to the heart may develop [17]. Maculopapular exanthem (MPE) of mild or moderate severity is by far the most common manifestation of NIHR [13•]. Other exanthems, such as severe cutaneous adverse reactions (e.g., drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or acute generalized exanthematous pustulosis (AGEP)), are rather uncommon [18, 19]. Also, erythema exudativum multiforme, bullous fixed drug eruption, and pompholyx are exceptional and have been reported only in individual cases [19].

## Mechanisms of RCM hypersensitivity

Until several years ago, the mechanism has been considered non-allergic. During the last years, we began to believe that RCM reactions may have an immunological basis and be allergic [20]. Evidence to support the hypothesis that patients with severe anaphylaxis primarily have an immunoglobulin E (IgE)-mediated allergic mechanism for IHR to RCM is accumulating [21••]. In support, a prospective study reported allergy as demonstrated by positive skin test in one in tenth, a quarter, half, and all patients with cutaneous, moderate-systemic, life-threatening anaphylaxis, and cardiac arrest, respectively [2•]. Further evidence for such an IgE- or mast cell-mediated mechanism includes positive skin tests, tryptase and histamine release during the reaction, and basophil activation tests [20]. However, still in the majority of patients with IHR of mild to moderate severity, no sensitization can be demonstrated; in those skin or basophil activation tests to RCM, possible indirect means of demonstrating allergy remain negative and a non-allergic mechanism is still assumed. A mechanism for non-allergic RCM reactions, which is demonstrable selectively in reacting patients, but not in tolerant controls, yet has been demonstrated [20]. In a mouse model, the RCM iopamidol activated the mast cell-specific receptor MRGPR X2 [22•].

The mechanism of NIHRs to RCM is T-cell mediated evidenced by a typical time of onset of delayed allergic reactions, by the clinical picture and the duration of the exanthem closely resembling other drug exanthems, as well as by positive patch and delayed readings of intradermal tests, ex vivo activated T-cells in positive skin test sites and by positive lymphocyte transformation tests (LTT) [4]. An underlying type IV T-cellular allergic mechanism often can be demonstrated by positive delayed skin tests, particularly in clearly defined and early tested patients, but is not always present [4, 23, 24••]. The responsible allergic structure within the RCM molecule is its benzene ring in the majority of patients and not the iodine ion. Positive skin tests to iodine or positive provocation tests with Lugol's solution have only been reported rarely in non-immediate reactions [24••, 25]. However, in individual patients with maculopapulous exanthem, iodine hypersensitivity may be present and

these may be identified by open repeated application test of iodine solution even without provocation [24••].

## Diagnostic workup of patients with RCM hypersensitivity

### Indication for testing

Not all patients with reported adverse reactions after receiving RCM profit from allergological workup [26••]. Those who only experienced subjective symptoms, particularly if only one symptom, e.g., feeling of warmth or erythema on injection side, nausea, paresthesia, headache, or dizziness or onset of other nonspecific symptoms between 1 and 6 h after the administration, most likely did suffer from a non-severe toxic reaction or causally unrelated reaction and will not show positive skin tests. Prescreening unselected patients by skin testing does not predict future hypersensitivity reactions [27•]. On the other hand, in patients reporting urticaria/angioedema/bronchospasm or suspicion of anaphylaxis occurring immediately and patients with exanthems presenting after 6 h to 7 days consistent with NIHR, there is an indication for allergy workup (Table 1) [26••].

### Skin testing of patients

The best time point for skin testing patients with RCM hypersensitivity is unknown. However, as skin tests 2–6 month after IHR and NIHR have shown best sensitivity in one multicenter study, this time interval is recommended also for allergy testing, although positive skin tests several years after the incident have been described in individual patients [11]. Although in Europe, skin testing has been reported to be helpful for diagnosing RCM hypersensitivity, this has only recently increasingly been consented by experts also in the USA [28•, 29]. It has been hypothesized that skin testing differentiates allergy from non-allergic reactions, and thus identifies a safe skin test-negative alternative, which has been confirmed by intravenous provocation [24••, 30].

The skin test procedure depends on the suspected mechanism [31•]. For IHR, skin prick tests (SPT) and intradermal tests (IDT) with immediate readings are done. For NIHR, patch test and late readings for SPT and IDT are crucial and will be added. In NIHR, IDT are more sensitive than patch tests. Skin tests are

**Table 1. Indications for allergy workup after reported adverse reactions to RCM**

Generalized cutaneous reaction: urticaria, angioedema, flushing
Isolated bronchospasm
Anaphylaxis
Delayed-appearing urticaria and angioedema (causal relationship questionable)
Maculopapular exanthema
Morphological variants of exanthema (e.g., fixed drug eruption, SDRIFE, AGEP)
Severe bullous skin reactions (SJS, TEN), severe systemic reaction (DRESS) (only skin tests, generally no drug provocation test, individual decisions possible)

*SJS* Stevens-Johnson syndrome; *TEN* toxic epidermal necrolysis; *FDE* fixed drug eruption; *DRESS* drug reaction with eosinophilia and systemic symptoms; *SDRIFE* symmetric drug-related intertriginous and flexural exanthema; *AGEP* acute generalized exanthematous pustulosis

performed with the culprit contrast agent and with a panel of alternative contrast agents (consider agents available in the institution performing future contrast imaging for the patient), if possible, for selecting a skin test-negative RCM for subsequent procedures [26••, 31•]. For IHR, RCM are recommended to be used undiluted at 300–320 mg/ml on the forearm or upper back for SPT as well as diluted at 1:10 for IDT. Testing should start by performing SPT and, if negative, be continued with IDT. In NIHR, IDT is done with 1:10 dilution of the standard concentration of RCM and delayed reading, e.g., after 48 and 72 h. Testing with undiluted RCM can be considered for higher sensitivity; however, immediate positive reactions could be irritative. In addition, a patch test on the upper back with undiluted standard solution of RCM with readings at 48 h and a further delayed reading (72–120 h) is recommended for optimal sensitivity. Although the sensitivity of late readings of IDT is by far higher than that of patch tests, in individual patients, patch tests exceptionally may be positive to a RCM with negative IDT. Thus, several centers prefer to test all their patients with IDT and patch tests in parallel. Validity of different reading times for skin tests has not yet been formally compared and patients should additionally be instructed to return for additional readings in case of any later appearing skin reaction at the test site [26••]. Although the IDT is more sensitive as compared to the patch test, using both tests may enhance sensitivity.

Sensitivity of skin tests appears to be higher, if the time interval between reaction and skin test is 2–6 months [11]. Also a higher rate of positive skin tests can be seen in more severe reactions [2•, 11]. In a meta-analysis, 52% of skin tests were positive in severe IHRs to RCM, whereas the rate dropped to 17%, if mild and moderate reactions were also included [21••]. In this analysis, 26% of patients with NIHR had positive skin tests. In the personal experience of the author, the rate is considerably higher, if patients with NIHR have been diagnosed in our department and tested within a few weeks afterwards. The specificity of skin tests is high: 95% for undiluted SPT, 91–96% for 1/10 diluted IDT in IHR and is considered to be close to 100% for all skin tests in NIHR [11, 21••]. Cross-sensitivity between RCM in skin testing and lymphocyte transformation test does occur and is higher in NIHR as compared to IHR [11, 32•]. The pattern of cross-reactivity of different RCMs has been analyzed and cross-reactivity of iobitridol to other RCM has been reported to be low in NIHR [32•, 33, 34•], which may be related to its R1 chain being different from that of other RCMs [35]. For IHR, the isoosmolar RCM iodixanol appears to have a low rate of IHRs, and among low osmolar RCM, some agents (e.g., iomeprol) have recently been associated with higher reaction rates than others (e.g., iohexol) [36, 37].

## Laboratory tests

During the immediate anaphylactic reaction, measuring increased tryptase levels in serum 1 to 4 h after the onset of the reaction can confirm the diagnosis of anaphylaxis, if levels increase sufficiently in comparison to baseline serum tryptase levels [38]. Measurements of increased histamine levels a few minutes after reaction onset is less practicable because of difficulties in probe handling, and lower availability of the commercial assay. The basophil activation test (BAT) has been reported to confirm the diagnosis of IHR to RCM in few studies [39–41]. Specificity was high and has been estimated 88.4–100%, whereas sensitivity was moderate (46–62%) [39, 40]. In NIHR, lymphocyte

transformation tests (LTT) may be positive and RCM-reactive T cell-lines and clones have been isolated for experimental purposes, but appear to have a lower sensitivity as compared to skin tests [42].

### Drug provocation test (DPT)

DPT with RCM has come up in the recent years and generally has been shown to be safe in the hands of experienced centers, although available protocols still are diverse and require standardization. Intravenous DPT can be either done with the skin test-negative culprit to exclude RCM allergy in a questionable causality or with an alternative skin test-negative RCM to find a substitute to be checked for tolerance, and which then can be used in the next contrasted imaging procedure [26••]. For DPT, adequate safety precautions should be taken and it should be done in an experienced setting. Still different protocols are used for DPT without consensus [24••, 32•, 33, 39, 43•, 44]. On the other hand, studies have shown that re-exposure of an alternative skin test-negative RCM is quite safe, if a RCM examination is needed. That brings up the question, when DPT in contrast to re-exposition is required. Performing DPT may be particularly considered in patients with severe anaphylaxis using a skin test-negative alternative substance. It is contraindicated in a patient with renal insufficiency, hyperthyroidism, radioactive iodine therapy, pregnant, and breast-feeding women [26••]. RCM-induced nephropathy has to be avoided [45]. The decision needs to be taken based on a risk-benefit analysis of each patient.

## Management of patients with RCM hypersensitivity

### In urgent need of RCM

Different principal options dependent on the principal need for and urgency for RCM imaging are available for patients with previous RCM hypersensitivity reactions from total avoidance to drug provocation test with skin test-negative RCM (Table 2). If patients with a history of RCM hypersensitivity have an immediate and urgent need of another RCM-based imaging and no suitable imaging alternative (e.g., magnet resonance tomography, native CT- or MR-scan) is available, in patients with mild IHR (urticaria ± angioedema) or mild NIHR (maculopapular exanthem), imaging with a non-culprit RCM can be considered under emergency preparedness and after premedication, because of the low risk of an allergic reaction and because premedication suppresses the majority of non-allergic reactions, which generally are of mild or moderate severity (Fig. 1) [26••, 31]. As it has been reported that changing the RCM from the culprit to a different RCM in a patient with previous RCM reaction may be more effective than premedication with single dose antihistamine or with single dose corticosteroid, changing the RCM is recommended in all patients [46, 47]. Different premedication protocols have been published for IHR, and a protocol using a combination of H1-antihistamine (e.g., 50 mg diphenhydramine 1 h before application) and corticosteroids (e.g., 50 mg prednisone 13, 7, and 1 h before application) is often cited and may be considered) [28•]. The efficiency of premedication is likely to be low, mostly effective in suppressing non-allergic non-severe reactions and may be given considering risk (adverse effects)/benefit (possible small reduction of reaction frequency and severity, particularly mild reactions) ratio for patients. In diabetic patients, postprocedure surrogate markers of adverse events (blood pressure,

**Table 2. Management options in patients with prior hypersensitivity reaction (HR) to iodinated radiocontrast media (RCM) (adapted from [26••])**

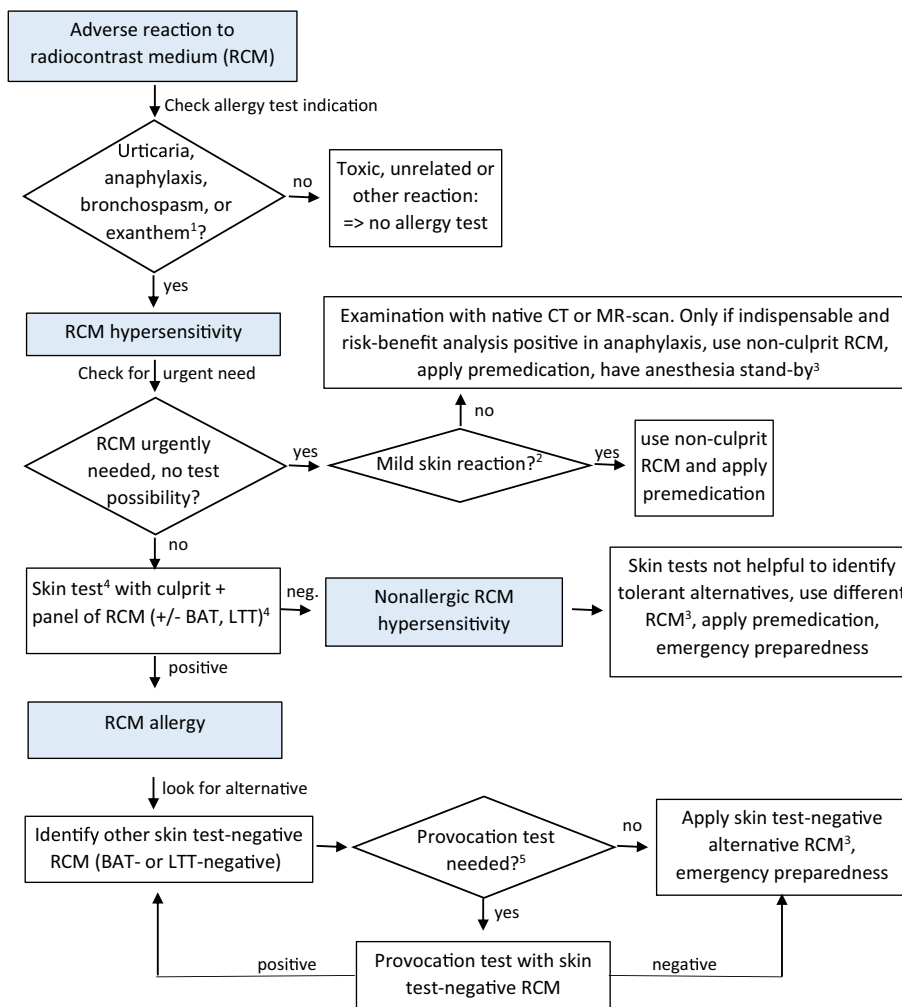
Management	Advantages	Disadvantages	Patient selection
Avoidance	Safety	RCM examination may be urgently needed Diagnosis unresolved	Patients with other diagnostic options (e.g., magnet resonance tomography) Patients without urgent need for RCM
Premedication	Well-established Reduces reaction rate particularly of non-severe reactions	Probably not helpful to prevent severe allergic HR Breakthrough reactions False sense of security Different regimes Risk of adverse effects to premedication	Patients with non-allergic reactions without positive skin test Patients where skin tests cannot be performed Patients with very severe reactions as an additional safety measure
Use of a non-culprit alternative by history	Easy Reduction of reaction rates demonstrated	Weak evidence Cross-reactivity not well studied	Patients with immediate urgent need of RCM without possibility of skin tests Patients with non-severe probable toxic reactions
Use of ST-negative alternative RCM	Good negative predictive value Omission of skin-test positive RCM with high risk of anaphylaxis	Only few patients with IHR have positive ST No benefit for non-allergic reactions Expertise needed Time consuming	All patients with suspicion of IHR or NIHR in whom skin tests can be performed

glucose levels, medication use) were increased after RCM administration with premedication [48]. The setting should be as safe as possible, e.g., taking place in hospitals with code teams and with close observation (possibly using pulseoxymetry). Mastocytosis does not appear to be associated with a higher frequency of IHRs [49]. It has been reported that reducing injection speed and using lower dose are associated with a lower relative risk of an IHR to RCM [50•]. Also, extrinsic warming of the RCM was associated with a reduced IHR rate [51•]. These measures may be applied to further reduce the reaction risk.

In patients with urgent need, but severe anaphylaxis, RCM should be best avoided and an allergological workup is necessary, if there is no imaging alternative. If RCM is considered indispensable, after a risk-benefit analysis, one may choose nevertheless to administer the non-culprit RCM, but only after premedication and with emergency preparedness including anesthesia standby. In this specific setting of immediate need, also desensitization may be considered, whereas in all other patients, proper allergy workup with skin tests and DPT is preferable and normally sufficient [52, 53]. In patients with severe NIHR possibly beyond medical control, RCM avoidance and other alternative procedures have to be looked for even in case of urgent need.

### After allergy workup

For patients without immediate need for contrasted imaging, an allergy workup is recommended (Fig. 1). In patients with IHR being skin test-positive to the



**Fig. 1.** Management of patients with previous radiocontrast medium reaction (adapted from [31•]). <sup>1</sup>Including exanthem variants, however, after severe bullous exantheams or after reactions with systemic symptoms skin test can be done, but future total RCM avoidance is normally recommended; <sup>2</sup>such as urticaria or “benign” maculopapular exanthema; <sup>3</sup>not after severe bullous exantheams or after drug reaction with systemic symptoms: here RCM avoidance; <sup>4</sup>BAT= basophil activation test, and LTT= lymphocyte transformation test may be helpful in some cases; <sup>5</sup>this is decided on a risk-benefit analysis, e.g. in patients with higher risk and more severe reactions in experienced allergy centers.

culprit RCM, a skin test-negative alternative can be administered without premedication under emergency preparedness and tolerance is expected. This strategy was successful in a number of studies [24••, 30, 54•], with only few others reporting different results [55]. Applying premedication can be considered in very severe IHRs, but its efficacy is unclear and adverse effects have to be considered. The culprit should be avoided as well as other skin test-positive RCMs. If available, BAT or LTT may supplement skin testing to select a RCM for future use, although cutoff values for positivity remain largely unvalidated. Whether DPT is advisable or direct re-exposition is preferable can be decided on an individual basis, e.g., depending on the severity of the reaction and



availability of DPT. A negative DPT with a skin test-negative agent has a high negative predictive value of > 90% in the real life setting [54, 56]. In patients with negative skin tests to the culprit and alternatives, a non-culprit RCM under emergency preparedness can be applied with premedication considered, as this appears to be particularly effective in the prevention of non-severe manifestations.

Contraindications for the further use of RCM may be those with very severe anaphylaxis after risk-benefit analysis and after severe bullous or systemic NIHR. However, these patients are very rare, and in the vast majority of patients, allergy testing in addition to changing the RCM substantially helps to increase safety of subsequent RCM exposures in patients with previous RCM hypersensitivity.

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## Declarations

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### Conflict of Interest

Knut Brockow declares that he/she has no conflict of interest.

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