

News and commentaries

Management of hypersensitivity reactions to iodinated contrast media

All iodinated contrast media (CM) are known to cause both immediate (≤ 1 h) and nonimmediate (> 1 h) hypersensitivity reactions. Although for most immediate reactions an allergic hypersensitivity cannot be demonstrated, recent studies indicate that the severe immediate reactions may be IgE-mediated, while most of the nonimmediate exanthematous skin reactions, appear to be T-cell mediated. Patients who experience such hypersensitivity reactions are therefore advised to undergo an allergologic evaluation. Several investigators have found skin testing to be useful in confirming a CM allergy, especially in patients with nonimmediate skin eruptions. If a patient with confirmed allergy to a CM needs a new CM exposure, a skin test negative CM should be chosen and premedication may be tried. However, none of these precautional measures is a guarantee against a repeat reaction. More research focusing on pathomechanisms, diagnostic testing and premedication is therefore clearly needed in order to prevent CM-induced hypersensitivity reactions in the future.

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Introduction

The adverse events seen after contrast media (CM) administration may be divided into three different types: (i) allergic and nonallergic hypersensitivity reactions as defined by the European Academy of Allergy and Clinical Immunology (1), (ii) toxic reactions (2) and (iii) events unrelated to CM exposure (Fig. 1). Hypersensitivity reactions are either immediate reactions, which occur within 1 h after CM administration, or nonimmediate reactions, which become apparent more than 1 h after CM exposure (3). About 70% of the immediate symptoms are reported to start within the first 5 min of CM administration (4).

This paper summarizes current state of the art regarding pathomechanisms, diagnosis and prevention of CM-induced hypersensitivity reactions and outlines open fields for further research in this area.

Prevalence of contrast medium reactions

Three large observational studies conducted in the mid-1980s indicated that mild adverse reactions of the immediate type occur in 3.8–12.7% of patients receiving intravenous injections of high-osmolar, ionic CM and in

0.7–3.1% of patients receiving low-osmolar nonionic CM (4–6). Severe immediate reactions have been reported to occur with a frequency of 0.1–0.4% for ionic CM and with a frequency of 0.02–0.04% for nonionic CM (4–7). Although the adverse reactions observed with the nonionic CM are usually less severe than the reactions induced by the ionic CM, the death rates for the two types of products are not significantly different. The mortality rate has been estimated to be in the range of 1 in 100 000 examinations (7). Severe and fatal reactions represent a serious problem in regard to the more than 70 million applications of CM per year worldwide (8).

The frequency of nonimmediate adverse reactions was recently reviewed by Webb et al. (9). In the 10 studies cited in this paper, the frequency ranged from 0.5 to 23%. This large variation may be due to the difficulty in verifying whether symptoms occurring hours or days after CM exposure are in fact caused by the CM. When radiological examinations with use of CM were compared with examinations without CM, most nonimmediate symptoms except skin reactions were found to be unrelated to the CM administration (10, 11). Thus, various types of exanthema seem to account for the majority of the CM-induced nonimmediate hypersensitivity reactions. Such eruptions have been reported to affect some 1–3% of CM-exposed patients (3, 11–13).

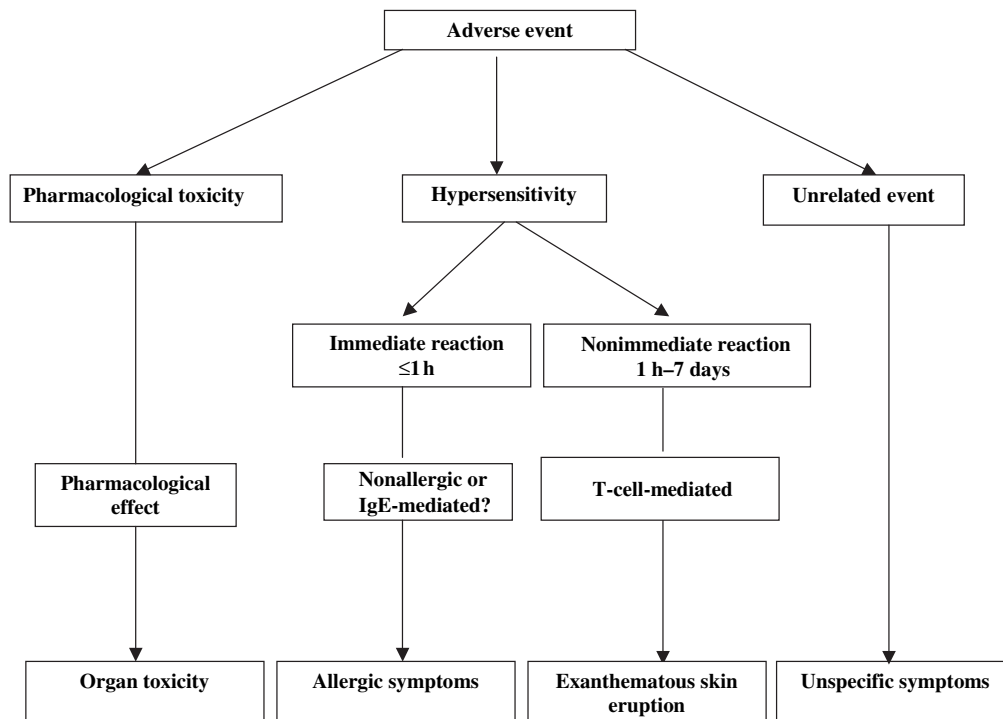


Figure 1. Classification of adverse events after contrast medium administration.

Table 1. Symptoms of immediate and nonimmediate hypersensitivity reactions to iodinated contrast media

Immediate reactions	Nonimmediate reactions
Pruritus	Pruritus
Urticaria	Urticaria
Angioedema	Angioedema
Flush	Exanthema (macular, maculopapular eruption)
Nausea, diarrhea, cramping	Erythema multiforme minor
Rhinitis (sneezing, rhinorrhea)	Fixed drug eruption
Hoarseness, cough	Stevens–Johnson syndrome
Dyspnea (bronchospasm, laryngeal edema)	Toxic epidermal necrolysis
Hypotension, tachycardia, arrhythmia	Graft-vs-host reaction
Cardiovascular shock	Vasculitis
Cardiac arrest	
Respiratory arrest	

Clinical symptoms

Clinical symptoms of hypersensitivity reactions to CM are listed in Table 1. Pruritus and mild urticaria are the commonest immediate manifestations, occurring in up to 70% of affected patients (4). More severe reactions involve the respiratory and cardiovascular systems, and most fatal hypersensitivity reactions to CM are immediate anaphylactic reactions (4–7).

The most frequent CM-induced nonimmediate reaction is maculopapular rash, observed in more than 50% of nonimmediate reactors (12). Other frequently occurring nonimmediate reactions include erythema, urticaria, angioedema, macular exanthema or scaling skin eruption (12–15). The nonimmediate skin reactions are usually mild to moderate in severity and transient and self-limiting. However, cases of severe skin reactions, such as Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and cutaneous vasculitis have been reported (14). Nonimmediate reactions with more immediate-type symptoms such as angioedema of the face combined with hypotension and/or dyspnea have been described occasionally (16, 17) and in a few patients, a biphasic reaction has been observed (18, 19). However, in general, no relationship between the occurrence of immediate and nonimmediate reactions has been found (12, 20, 21).

Risk factors

The most significant risk factor for an immediate hypersensitivity reaction is a previous immediate reaction. Previous reactors have a 21–60% risk of a repeat reaction when re-exposed to the same or a similar ionic CM (4, 22–24). When patients with a previous reaction to an ionic CM are subsequently given a nonionic CM, an up to 10-fold reduction in the incidence of severe repeat

reactions has been reported (24). No data are presently available regarding the frequency of repeat reactions to nonionic CM in patients with previous reaction to a nonionic CM.

Other risk factors for more severe immediate reactions are severe allergy, bronchial asthma, cardiac disease and treatment with beta-blockers (4, 22, 25–27).

Reported predisposing factors for nonimmediate skin reactions are a previous CM-induced adverse reaction, interleukin-2 treatment, serum creatinine level > 2.0 mg/dl and a history of drug and contact allergy (12, 20, 21, 28).

Other potential factors that may influence the severity of a CM reaction include mastocytosis, viral infection at time of CM exposure and autoimmune diseases, such as systemic lupus erythematosus (29, 30).

Pathophysiology

Immediate hypersensitivity reactions to CM are at least in part associated with histamine release from basophils and mast cells (31). Histamine release may be due to (i) a direct membrane effect related to the osmolality of the CM solution or the chemical structure of the CM molecule, (ii) an activation of the complement system or (iii) an IgE-mediated mechanism. Evidence for an IgE-mediated reaction has mainly been found in the rare cases of severe reaction (31–41).

Most of the CM-induced nonimmediate skin eruptions appear to be T-cell mediated allergic reactions as shown by (i) the frequently reported positive patch tests (PT) and delayed intradermal tests (IDT) to the culprit CM in previous reactors (18, 42–58), (ii) the presence of dermal infiltrates of T cells in affected skin and positive skin test sites (42–49, 54, 56, 58–60), (iii) the reappearance of the eruption after provocation testing (45–47), and (iv) the ability of CM to stimulate proliferation of peripheral T cells from patients with CM-induced skin eruptions (53, Pichler et al. unpublished data).

Clinical diagnosis

History and clinical evaluation

The ENDA questionnaire may be useful in obtaining the most important information regarding the patient's history and clinical manifestations of the adverse reaction (61). One important piece of information is the interval between CM administration and the onset of symptoms, required in order to classify the reaction as either immediate (≤ 1 h) or nonimmediate (> 1 h). The severity of the reaction should also be documented. For assessing the severity of immediate hypersensitivity reactions, the scoring system of Ring and Messmer (Table 2) has proved helpful (62). The severity of nonimmediate skin reactions may be graded as mild when no treatment is

Table 2. Severity of immediate hypersensitivity reactions to iodinated contrast media (62)

Grade	Symptoms			
	Skin	Abdomen	Respiratory tract	Circulation
I	Pruritus Flush Urticaria Angioedema			
II	Pruritus Flush Urticaria Angioedema	(not obligatory) Nausea Cramping	Rhinorrhea Hoarseness Dyspnea	Tachycardia ($\Delta > 20$ /min) Hypotension ($\Delta > 20$ mmHg syst.) Arrhythmia
III	Pruritus Flush Urticaria Angioedema	(not obligatory) Vomiting Defecation Diarrhea	Laryngeal edema Bronchospasm Cyanosis	Shock
IV	Pruritus Flush Urticaria Angioedema	(not obligatory) Vomiting Defecation Diarrhea	Respiratory arrest	Circulatory arrest

required, moderate when the patient responds readily to appropriate treatment and no hospitalization is needed, or severe when the reaction requires treatment in hospital, is life-threatening or results in death.

Diagnosis of immediate hypersensitivity reactions

During or immediately after the reaction

Plasma histamine and tryptase. Elevated serum levels of histamine and tryptase have been found in some but not all patients with severe or fatal immediate reactions but not in those with milder symptoms (31, 32, 34, 41, 63). The usefulness of these markers for diagnostic purposes remains to be established.

Plasma histamine concentration is known to peak within 5–10 min after onset of symptoms, and for patients with reactions of lower severity grade, histamine may return to baseline level in <1 h (31). Consequently, blood samples for histamine analysis should be drawn as soon as possible after the reaction. For tryptase, blood sampling 1–2 h after onset of symptoms has been recommended (64). To enable comparison with baseline levels, new blood samples should be collected 1–2 days after the reaction.

After recovery

Skin tests. Skin prick tests (SPT) and IDT have been performed for many years in the diagnosis of immediate hypersensitivity reactions to CM, but positive tests have only rarely been reported and only in patients with severe reactions (31, 34–38, 40, 41).

Most investigators have performed skin testing with undiluted CM for SPT and with CM diluted 1/1000 to

1/10 for IDT. Only two groups of investigators have reported results from intradermal testing of negative controls (36, 37). Both groups found no positive IDT to CM diluted 1/100 when tested in 20 and 25 healthy controls, respectively. Hence, there is a need to establish whether more concentrated CM solutions remain nonirritative. Also the sensitivity of these tests in detecting an occasional IgE-mediated reaction remains to be determined.

Specific IgE antibodies. Three groups of investigators have reported the presence of CM-specific IgE antibodies in the serum of patients with immediate reaction (31–33, 39). The reported frequency of positive test results varies widely. While a Japanese group detected CM-specific IgE to ioxaglate in 47% of immediate reactors (32), a French group found CM-specific IgE to either ioxaglate or ioxithalamate only in the 2–3% of reactors with severe symptoms (35).

No commercial assay is available for routine measurement of serum levels of CM-specific IgE antibodies, and the value of the test in diagnosis of severe immediate reactions remains to be established.

Basophil activation. Dose-dependent, direct histamine release was demonstrated when human peripheral blood leukocytes were incubated for 30–60 min at 37°C in presence of rather high concentrations of CM (20–400 mM) (65–68). Leukocytes from atopic individuals were reported to release more histamine upon CM exposure than leukocytes from nonatopics (67). The CM-induced *in vitro* histamine release was also reported to be significantly higher for previous CM reactors as compared with patients without previous reaction or healthy volunteers (68).

The role of the histamine release test and other *in vitro* basophil activation tests in the allergy diagnosis of reactions to CM is not yet defined.

Provocation test/pretesting procedure. In the 1970s, a 0.5–1 ml test dose of undiluted CM was often given intravenously 2–5 min before the radiological procedure in an attempt to avoid severe reactions to the subsequent full dose of CM. However, such pretesting may elicit severe reactions and gives a false sense of security (69–71).

A different protocol using graded challenge testing of patients with a history of immediate reactions to CM has been reported by Yocum et al. (23). They administered 0.1 ml test doses of 10-fold dilutions at 15-min intervals starting with 1/10 000 up to undiluted CM, followed by 1 and 5 ml of the undiluted CM before performing the examination. Positive reactions of mild to moderate severity were seen in 22% of patients with a definite history of immediate hypersensitivity reaction to CM. In half of the pretest-positive patients, the full dose of CM was subsequently given with or without premedication, and these patients reacted significantly more frequently as compared with pretest-negative patients with or without premedication. Although this procedure appears to be effective in identifying high-risk patients, it is unsuited for routine use because of the time consuming nature of the protocol.

Diagnosis of nonimmediate hypersensitivity reactions

During or immediately after the reaction

Hematology and clinical chemistry. In patients with CM-induced nonimmediate skin eruptions, other organs may be involved (49). Thus, during the acute phase of more severe reactions, laboratory tests such as liver and renal function tests as well as differential blood cell counts to look for eosinophilia should be considered. No data are presently available regarding the frequency of laboratory test abnormalities in these patients.

In addition to the above routine laboratory tests, tests for the presence of lymphocyte activation markers (e.g. CD25, CD69, HLA-DR by flow cytometry or soluble CD25 by enzyme immunoassay) may be conducted to search for the participation of activated T cells in these reactions. Such tests must be regarded as research tools.

Skin biopsy. Histological examination of biopsy samples from nonimmediate skin eruptions has occasionally been conducted. In cases of fixed drug eruption (FDE), the affected skin showed lymphocyte infiltration of the dermis and epidermis, epidermal spongiosis and necrosis, as well as hydropic degeneration of the basal layer (42, 43, 59). Other reported findings were neutrophilic abscess within the stratum corneum and pronounced eosinophilic degeneration. In a case of SJS, a severe lymphohistiocytic

infiltrate throughout the dermis and focal epidermal necrosis with blister formation were observed (60), while in a case of acute vasculitis the biopsy showed leukocytoclasia and a peripheral infiltrate of neutrophils around vessels (72). Maculopapular skin eruptions present with perivascular infiltration of lymphocytes in the dermis, sometimes accompanied with intraepidermal spongiosis and dermal infiltrates of eosinophils and/or histiocytes (44, 46–49).

Histological examination of skin biopsies can be of value in the pathophysiological evaluation of the reaction. But unfortunately, biopsy findings in exanthematous drug eruptions have few typical features (e.g. eosinophilia), which can aid in the differentiation of a drug eruption from other skin eruptions. Thus, a skin biopsy sample can be taken, but the results have to be interpreted together with other clinical information.

After recovery

Skin tests. Positive PT to undiluted CM after 1–4 days have been described in patients with macular or maculopapular exanthema, FDE, erythema multiforme, urticaria-like eruption and TEN (18, 42–44, 46, 47, 50–55, 57, 58). Although PT appear to be specific, based on the reported negative test results in 30 healthy controls (49, 53), there is presently no data on the sensitivity of this test.

Several investigators have reported positive delayed IDT to undiluted or diluted CM in patients with nonimmediate skin reactions (18, 43–45, 49, 52–54, 56, 57). Erythematous plaques become apparent at the test sites after a period of 1–3 days. Often patients had positive tests to several CM (18, 48, 49, 52–54, 57). Delayed IDT is reported to be more sensitive than PT, but also IDT may sometimes be falsely negative as indicated in a recent case series (57).

SPT with undiluted CM have in few cases resulted in erythematous palpable plaques after 1–3 days (45, 47), but this test is much less sensitive than both PT and IDT (53, 57).

In summary, PT with undiluted CM on the back with readings after 2 and 3–4 days, and IDT with diluted CM and late readings after 1–3 days appear to be specific and useful in allergy diagnosis of nonimmediate skin reactions to CM. Both PT and IDT should be read after 1 week, if previously negative (73). For safety reasons, SPT with undiluted CM and reading after 15–20 min should be conducted before performing IDT.

The optimal CM concentration for use in IDT remains to be established, and the sensitivity of both PT and IDT has to be investigated.

Lymphocyte transformation test. Although LTT has occasionally been used in diagnosis of nonimmediate hypersensitivity (53), this test cannot be recommended for routine use at present.

Provocation test. Provocation testing to confirm a non-immediate CM allergy has only been described in three case reports (45–47). Testing with progressive increase of the injected CM dose over several days may be useful to confirm a negative skin test result before the patient is exposed to the full dose of CM (57, 59). However, because of the potential risk involved it remains a research procedure.

Prophylaxis

Prevention of immediate reactions

Contrast medium selection. In patients with risk factors such as bronchial asthma or previous CM-induced immediate adverse reaction, radiologists have routinely administered low-osmolar CM because of their lower incidence of total reactions (74, 75). If a patient with a previous immediate hypersensitivity reaction to a CM needs a new CM exposure, the CM that caused the reaction should not be readministered. New exposure to CM should be avoided in patients with previous severe CM-induced immediate reaction.

So far, only three case reports have described the successful use of skin tests or *in vitro* basophil activation test for selection of a safe, alternative CM in patients with previous immediate reaction (34–36). Results from larger multi-center studies are needed in order to clarify the usefulness of these tests as routine tools.

Premedication. It has been common practice to use premedication with corticosteroids either alone or in combination with H1-antihistamines and/or H2-antihistamines in patients with a history of moderate or severe immediate reaction to CM (74, 75). In the recent guidelines from European Society of Urogenital Radiology on prevention of generalized contrast medium reactions, prednisolone (30 mg) or methylprednisolone (32 mg) orally 12 and 2 h before contrast medium exposure was recommended in high risk patients (74). However, severe CM-induced anaphylactic reactions have occurred in previous reactors despite such prophylactic use of corticosteroids (76–79). Therefore, the exact role of premedication needs to be further established.

Prevention of nonimmediate reactions

Contrast medium selection. Patients with previous CM-induced nonimmediate skin eruptions are at risk for developing new eruptions if re-exposure to the same CM takes place (43, 47, 48, 50, 53, 55, 58). Consequently, another CM product should be chosen if re-exposure is required. Because of frequent cross-reactivity between different CM, change of CM is no guarantee against a repeat reaction.

Several investigators have used PT and delayed IDT to confirm an allergic reaction to the culprit CM in this group of patients. However, it remains to be established if skin testing is also a suitable tool for selection of an alternative CM that can subsequently be safely used. At present the administration of skin test negative CM in previous reactors should be done with caution as reactions have been observed after administration of skin test negative CM (57).

Premedication. In the recent guidelines from the Contrast Media Safety Committee of the European Society of Urogenital Radiology, it is stated that patients with previous serious nonimmediate adverse reactions can be given oral steroid prophylaxis if new CM exposure is required (9). However, no studies have so far been conducted to establish the optimum pretreatment regimen. Repeated nonimmediate reactions, including a case of TEN, have been reported despite corticosteroid premedication (16, 48, 50, 53, 55, 58, 80).

A different pretreatment protocol was recently described by Romano et al. (53). They reported the successful use of intramuscular 6-methyl-prednisolone (40 mg daily) and oral cyclosporine (100 mg twice daily) 1 week before and 2 weeks after each of four angiograms in a patient with two previous episodes of maculopapular reaction after CM administration, the last despite steroid premedication.

Further investigations are needed in order to establish a practical and effective pretreatment protocol for prevention of new reactions in patients with previous nonimmediate skin reactions to CM.

Conclusion

There has been remarkable progress in the understanding of the pathophysiology of CM-induced hypersensitivity reactions in the last decade. Current evidence indicates that both severe immediate reactions and nonimmediate skin eruptions may be allergic reactions, involving

Table 3. Future research agenda for hypersensitivity reactions to contrast media (CM)

Search for new risk factors
Optimization of skin test conditions
Determination of sensitivity and specificity of standardized skin tests in the diagnosis of CM allergy
Establishment of the value of skin tests for the selection of an alternative, safe CM for use in previous reactors
Development and/or validation of <i>in vitro</i> diagnostic tests, such as CM-specific IgE antibody test, basophil and lymphocyte activation tests and lymphocyte transformation tests
Elucidation of the pathomechanism of non-IgE-mediated immediate hypersensitivity reactions
Establishment of the role of premedication in prevention of severe CM reactions

CM-reactive IgE and T cells, respectively. Skin testing has been used to confirm a CM allergy in patients with such reactions. However, the specificity and sensitivity of these tests remain to be established. *In vitro* tests to search for CM-specific IgE or T cells are currently under investigation and must be regarded as research tools at present. In patients with previous severe reactions current premedication procedures appear to reduce symptoms but may not prevent repeat reactions. In conclusion, further research in the area of CM-induced hypersensitivity

reactions is strongly needed in order to answer still open questions regarding the pathophysiology, diagnosis and prevention of these reactions (Table 3).

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References

- Johansson SG, Hourihane JO, Bousquet J, Brujinzeel-Koomen C, Dreborg S, Haahtela T et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;**56**:813–824.
- Almén T. The etiology of contrast medium reactions. *Invest Radiol* 1994;**29**:S37–S45.
- Munehika H, Hiramatsu Y, Kudo S, Sugimura K, Hamada C, Yamaguchi K et al. A prospective survey of delayed adverse reactions to iohexol in urography and computed tomography. *Eur Radiol* 2003;**13**:185–194.
- Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. *Radiology* 1990;**175**:621–628.
- Wolf GL, Arenson RL, Cross AP. A prospective trial of ionic vs nonionic contrast agents in routine clinical practice: Comparison of adverse effects. *Am J Roentgenol* 1989;**152**:939–944.
- Palmer FJ. The RACR survey of intravenous contrast media reactions. Final report. *Australas Radiol* 1988;**32**:426–428.
- Caro JJ, Trindade E, McGregor M. The risks of death and of severe nonfatal reactions with high- vs low-osmolality contrast media: a meta-analysis. *Am J Roentgenol* 1991;**156**:825–832.
- Christiansen C. X-ray contrast media – an overview. *Allergologie* 2004;**27**:165 (abstract no. 57).
- Webb JA, Stacul F, Thomsen HS, Morcos SK. Late adverse reactions to intravascular iodinated contrast media. *Eur Radiol* 2003;**13**:181–184.
- Schild H. Delayed allergy-like reactions in patients: monomeric and dimeric contrast media compared with plain CT. *Eur Radiol* 1996;**6** (insert to issue 5): 9–10.
- Yasuda R, Munehika H. Delayed adverse reactions to nonionic monomeric contrast-enhanced media. *Invest Radiol* 1998;**33**:1–5.
- Hosoya T, Yamaguchi K, Akutsu T, Mitsuhashi Y, Kondo S, Sugai Y et al. Delayed adverse reactions to iodinated contrast media and their risk factors. *Radiat Med* 2000;**18**:39–45.
- Rydberg J, Charles J, Aspelin P. Frequency of late allergy-like adverse reactions following injection of intravascular non-ionic contrast media. A retrospective study comparing a non-ionic monomeric contrast medium with a non-ionic dimeric contrast medium. *Acta Radiol* 1998;**39**:219–222.
- Christiansen C, Pichler WJ, Skotland T. Delayed allergy-like reactions to X-ray contrast media: mechanistic considerations. *Eur Radiol* 2000;**10**: 1965–1975.
- Sutton AG, Finn P, Grech ED, Hall JA, Stewart MJ, Davies A et al. Early and late reactions after the use of iopamidol 340, ioxaglate 320, and iodoxanol 320 in cardiac catheterization. *Am Heart J* 2001;**141**:677–683.
- Savader SJ, Brodtkin J, Osterman FA. Delayed life-threatening reaction to non-ionic contrast media. *J Invest Radiol* 1995;**10**:115–116.
- Miyamoto Y, Tatei T, Ichijima S, Nakayama M, Oono K, Yamashita M. Delayed eruption caused by non-ionic contrast material injection. *J Jpn Radiol Assoc* 1990;**50**:295–297.
- Brockow K, Kiehn M, Kleinheinz A, Vieluf D, Ring J. Positive skin tests in late reactions to radiographic contrast media. *Allerg Immunol (Paris)* 1999;**31**:49–51.
- Stovsky MD, Seftel AD, Resnick MI. Delayed hypersensitivity reaction after infusion of nonionic intravenous contrast material for an excretory urogram: a case report and review of the literature. *J Urol* 1995;**153**:1641–1643.
- Choyke PL, Miller DL, Lotze MT, Whiteis JM, Ebbitt B, Rosenberg SA. Delayed reactions to contrast media after interleukin-2 immunotherapy. *Radiology* 1992;**183**:111–114.
- Yoshikawa H. Late adverse reactions to nonionic contrast media. *Radiology* 1992;**183**:737–740.
- Ansell G, Tweedie MC, West CR, Evans P, Couch L. The current status of reactions to intravenous contrast media. *Invest Radiol* 1980;**15**:S32–S39.
- Yocum MW, Heller AM, Abels RI. Efficacy of intravenous pretesting and antihistamine prophylaxis in radiocontrast media-sensitive patients. *J Allergy Clin Immunol* 1978;**62**:309–313.
- Wolf GL, Mishkin MM, Roux SG, Halpern EF, Gottlieb J, Zimmerman J et al. Comparison of the rates of adverse drug reactions. Ionic contrast agents, ionic agents combined with steroids, and nonionic agents. *Invest Radiol* 1991;**26**:404–410.
- Bettmann MA, Heeren T, Greenfield A, Goudey C. Adverse events with radiographic contrast agents: results of the SCVIR contrast agent registry. *Radiology* 1997;**203**:611–620.
- Lang DM, Alpern MB, Visintainer PF, Smith ST. Increased risk for anaphylactoid reaction from contrast media in patients on β -adrenergic blockers or with asthma. *Ann Intern Med* 1991;**115**:270–276.
- Lang DM, Alpern MB, Visintainer PF, Smith ST. Elevated risk of anaphylactoid reaction from radiographic contrast media is associated with both β -blocker exposure and cardiovascular disorders. *Arch Intern Med* 1993;**153**:2033–2040.
- Aoki Y, Takemura T. Allergies correlated to adverse reactions induced by non-ionic monomeric and ionic dimeric contrast media for contrast enhanced CT examination. *Jpn J Radiol Technol* 2002;**58**:1245–1251.

29. Pichler WJ, Yawalkar N, Britschgi M, Depta J, Strasser I, Schmid S et al. Cellular and molecular pathophysiology of cutaneous drug reactions. *Am J Clin Dermatol* 2002;**3**:229–238.
30. Pichler WJ, Yawalkar N. Allergic reactions to drugs: involvement of T cells. *Thorax* 2000;**55**(Suppl. 2):561–565.
31. Laroche D, Aimone-Gastin I, Dubois F, Huet H, Gérard P, Vergnaud M-C et al. Mechanisms of severe, immediate reactions to iodinated contrast material. *Radiology* 1998;**209**:183–190.
32. Mita H, Tadokoro K, Akiyama K. Detection of IgE antibody to a radio-contrast medium. *Allergy* 1998;**53**:1133–1140.
33. Sweeney MJ, Klotz SD. Frequency of IgE mediated radio contrast dye reactions. *J Allergy Clin Immunol* 1983;**71**:147.
34. Dewachter P, Mouton-Faivre C, Felden F. Allergy and contrast media. *Allergy* 2001;**56**:250–251.
35. Wakkers-Garritsen BG, Houwerzijl J, Nater JP, Wakkers PJ. IgE-mediated adverse reactivity to a radiographic contrast medium. *Ann Allergy* 1976;**36**:122–126.
36. Kanny G, Maria Y, Mentre B, Moneret-Vautrin DA. Case report: recurrent anaphylactic shock to radiographic contrast media. Evidence supporting an exceptional IgE-mediated reaction. *Allerg Immunol (Paris)* 1993;**25**:425–430.
37. Patriarca G, Venuti A, Schiavino D, Romano A. Specific desensitizing treatment in allergy to iodine-containing contrast media: observation in one patient. *Ann Allergy* 1978;**40**:200–202.
38. Alvarez-Fernández JA, Valero AM, Pulido Z, de la Hoz B, Cuevas M, Sánchez-Cano M. Hypersensitivity reaction to ioversol. *Allergy* 2000;**55**:581–582.
39. Laroche D, Namour F, Lefrançois C, Aimone-Gastin I, Romano A, Sainte-Laudy J et al. Anaphylactoid and anaphylactic reactions to iodinated contrast material. *Allergy* 1999;**54**:13–16.
40. Moneret-Vautrin DA, Kanny G, Morisset M, Beaudouin E, Renaudin JM. Anaphylactoid reactions and late skin reactions to iodinated contrast media: present state of the question – development of ideas. *Rev Med Interne* 2001;**22**:969–977.
41. Laroche D, Dewachter P, Mouton-Faivre C, Clément O. Immediate reactions to iodinated contrast media: the CIR-TACI study. *Allergologie* 2004;**27**:165 (abstract no. 56).
42. Yamauchi R, Morita A, Tsuji T. Fixed drug eruption caused by iopamidol, a contrast medium. *J Dermatol* 1997;**24**:243–245.
43. Watanabe H, Sueki H, Nakada T, Akiyama M, Iijima M. Multiple fixed drug eruption caused by iomeprol (Iomeron®), a nonionic contrast medium. *Dermatology* 1999;**198**:291–294.
44. Brockow K, Becker EW, Worret W-I, Ring J. Late skin test reactions to radiocontrast medium. *J Allergy Clin Immunol* 1999;**104**:1107–1108.
45. Kanzaki T, Sakagami H. Late phase allergic reaction to a CT contrast medium (iotrolan). *J Dermatol* 1991;**18**:528–531.
46. Schick E, Weber L, Gall H. Delayed hypersensitivity reaction to the non-ionic contrast medium iopromid. *Contact Dermatitis* 1996;**35**:312.
47. Gall H, Pillekamp H, Peter R-U. Late-type allergy to the X-ray contrast medium Solutrast® (iopamidol). *Contact Dermatitis* 1999;**40**:248–250.
48. Otto K, Kaempgen E, Dummer W, Broecker E-B, Becker JC. Late-type allergy to Ultravist® (iopromid). *Allergy* 2003;**58**:261–262.
49. Kanny G, Marie B, Hoen B, Trechot P, Moneret-Vautrin DA. Delayed adverse reaction to sodium ioxaglic acid-meglumine. *Eur J Dermatol* 2001;**11**:134–137.
50. Rosado A, Canto G, Veleiro B, Rodríguez J. Toxic epidermal necrolysis after repeated injections of iohexol. *Am J Roentgenol* 2001;**176**:262–263.
51. Sedano E, Vega JM, Rebollo S, Callejo A, Asensio T, Almendros R. Delayed exanthema to nonionic contrast medium. *Allergy* 2001;**56**:1015–1016.
52. Erdmann S, Roos T, Merk HF. Delayed hypersensitivity reaction to the nonionic contrast medium ioversol. *Zeitschrift für Haut- und Geschlechtskrankheiten* 2000;**75**:169–171.
53. Romano A, Artesani MC, Andriolo M, Viola M, Pettinato R, Vecchioli-Scalazza A. Effective prophylactic protocol in delayed hypersensitivity to contrast media: report of a case involving lymphocyte transformation studies with different compounds. *Radiology* 2002;**225**:466–470.
54. Akiyama M, Nakada T, Sueki H, Fujisawa R, Iijima M. Drug eruption caused by nonionic iodinated X-ray contrast media. *Acad Radiol* 1998;**5**:S159–S161.
55. Courvoisier S, Bircher AJ. Delayed-type hypersensitivity to a nonionic, radio-paque contrast medium. *Allergy* 1998;**53**:1221–1224.
56. Christiansen C, Dreborg S, Pichler WJ, Ekeli H. Macular exanthema appearing 5 days after X-ray contrast medium administration. *Eur Radiol* 2002;**12**:S94–S97.
57. Vernassiere C, Trechot P, Commun N, Schmutz J-L, Barbaud A. Low negative predictive value of skin tests in investigating delayed reactions to radio-contrast media. *Contact Dermatitis* 2004;**50**:359–366.
58. Sánchez-Pérez J, F-Villalta MG, Ruiz SA, García Díez A. Delayed hypersensitivity reaction to the non-ionic X-ray contrast medium Visipaque® (iodixanol). *Contact Dermatitis* 2003;**48**:167.
59. Ángeles Gonzalo-Garijo M, de Argila D, Pimentel JJ, Alejo M, García-Menaya JM. Skin reaction to contrast medium. *Allergy* 1997;**52**:875–876.
60. Savill JS, Barrie R, Ghosh S, Muhlemann M, Dawson P, Pusey CD. Fatal Stevens–Johnson syndrome following urography with iopamidol in systemic lupus erythematosus. *Postgrad Med J* 1988;**64**:392–394.
61. Demoly P, Kropf R, Bircher A, Pichler WJ. Drug hypersensitivity: questionnaire. *Allergy* 1999;**54**:999–1003.
62. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* 1977;**1**:466–469.
63. Brockow K, Vieluf D, Püschel K, Grosch J, Ring J. Increased postmortem serum mast cell tryptase in a fatal anaphylactoid reaction to nonionic radiocontrast medium. *J Allergy Clin Immunol* 1999;**104**:237–238.
64. Laroche D, Vergnaud M-C, Sillard B, Soufarapis H, Bricard H. Biochemical markers of anaphylactoid reactions to drugs. Comparison of plasma histamine and tryptase. *Anesthesiology* 1991;**75**:945–949.
65. Assem ES, Bray K, Dawson P. The release of histamine from human basophils by radiological contrast agents. *Br J Radiol* 1983;**56**:647–652.
66. Ring J, Arroyave CM, Frizler MJ, Tan EM. In vitro histamine and serotonin release by radiographic contrast media (RCM). Complement-dependent and independent release reaction and changes in ultrastructure of human blood cells. *Clin Exp Immunol* 1978;**32**:105–118.
67. Siegle RL, Lieberman P, Jennings BR, Rice MC. Iodinated contrast material: studies relating to complement activation, atopy, cellular association, and antigenicity. *Invest Radiol* 1980;**15**:S13–S17.

68. Ring J, Simon RA, Arroyave CM. Increased in vitro histamine release by radiographic contrast media in patients with history of incompatibility. *Clin Exp Immunol* 1978;**34**:302–309.
69. Fischer HW, Doust VL. An evaluation of pretesting in the problem of serious and fatal reactions to excretory urography. *Radiology* 1972;**103**:497–501.
70. Witten DM, Hirsch FD, Hartman GW. Acute reactions to urographic contrast medium: incidence, clinical characteristics and relationship to history of hypersensitivity states. *Am J Roentgenol* 1973;**119**:832–840.
71. Yamaguchi K, Katayama H, Takashima T, Kozuka T, Seez P, Matsuura K. Prediction of severe adverse reactions to ionic and nonionic contrast media in Japan: evaluation of pretesting. A report from the Japanese Committee on the Safety of Contrast Media. *Radiology* 1991;**178**:363–367.
72. Goodfellow T, Holdstock GE, Brunton FJ, Bamforth J. Fatal acute vasculitis after high-dose urography with iohexol. *Br J Radiol* 1986;**59**:620–621.
73. Barbaud A, Goncalo M, Bruynzeel D, Bircher A. Guidelines for performing skin tests with drugs in the investigation of cutaneous adverse drug reactions. *Contact Dermatitis* 2001;**45**:321–328.
74. Morcos SK, Thomsen HS, Webb JA. Prevention of generalized reactions to contrast media: a consensus report and guidelines. *Eur Radiol* 2001;**11**:1720–1728.
75. Cohan RH, Ellis JH, Dunnick NR. Use of low-osmolar agents and premedication to reduce the frequency of adverse reactions to radiographic contrast media: a survey of the Society of Uroradiology. *Radiology* 1995;**194**:357–364.
76. Roberts M, Fisher M. Anaphylactoid reaction to iopamiro (after pretreatment). *Australas Radiol* 1992;**36**:144–146.
77. Madowitz JS, Schweiger MJ. Severe anaphylactoid reaction to radiographic contrast media. Recurrence despite premedication with diphenhydramine and prednisone. *JAMA* 1979;**241**:2813–2815.
78. Ketkar M, Shrier D. An allergic reaction to intraarterial nonionic contrast material. *Am J Neuroradiol* 2003;**24**:292.
79. Freed KS, Leder RA, Alexander C, DeLong DM, Kliewer MA. Breakthrough adverse reactions to low-osmolar contrast media after steroid premedication. *Am J Roentgenol* 2001;**176**:1389–1392.
80. Borofsky HB, Barnard CM, Lang EV. Fixed bullous drug eruption due to iohexol. *Adv X-Ray Contrast* 1993;**1**:58–60.