# Hypersensitivity Reactions to Contrast Media: Part 1. Management of Immediate and Non-immediate Hypersensitivity Reactions in Adults. Updated ESUR Contrast Media Safety Committee Guidelines

# ELECTRONIC SUPPLEMENTARY MATERIAL

**Online Supplement 1:** Original Literature Searches

*Literature Search IHR*

| Database | Search String |
|---|---|
| PubMed<br><br>1985 – May 2022 | ("Contrast Media"[Mesh] OR contrast medi* [tiab] OR contrast agent* [tiab] OR contrast material* [tiab] OR contrast dose [tiab] OR contrast doses [tiab] OR contrast dosage [tiab] OR radiocontrast medi* [tiab] OR radiocontrast agent* [tiab] OR radiopaque medi* [tiab] OR radiocontrast dose [tiab] OR radiocontrast doses [tiab] OR radiocontrast dosage [tiab] OR "Barium"[Mesh] OR barium [tiab] OR gadolinium [tiab] OR microbubble* [tiab])<br>AND (("Drug Hypersensitivity"[Mesh] OR hypersensitiv* [tiab] OR allergic* [tiab] OR anaphylaxis [tiab] OR anaphylact* [tiab] OR adverse reaction*[tiab] OR urticaria* [tiab] OR diffuse erythema [tiab] OR facial edema [tiab] OR angioedema [tiab] OR bronchospasm* [tiab] OR laryngeal edema [tiab] OR anaphylactic shock [tiab] OR hypotension [tiab] OR pulmonary edema [tiab] OR cardiac arrest [tiab] OR respiratory arrest [tiab]) AND (acute [tiab] OR after administration [tiab] OR rapid* [tiab] OR severe [tiab]))<br>AND (treatment [tiab] OR treat [tiab] OR recommend* [tiab])<br>AND ("english"[Language]) AND ("1985"[Date - Publication] : "3000"[Date - Publication]) |
| Embase (Elsevier) | contrast medium'/exp/mj OR (((contrast OR radiocontrast) NEAR/2 (medi* OR agent* OR material* OR dose OR doses OR dosage)):ab,ti) OR 'radiopaque medi*':ab,ti OR 'barium'/exp/mj OR barium:ab,ti OR 'gadolinium'/exp/mj OR gadolinium:ab,ti OR 'microbubble'/exp/mj OR microbubble*:ab,ti)<br>AND (('hypersensitivity'/exp OR hypersensitiv*:ab,ti OR allergic*:ab,ti OR anaphylaxis:ab,ti OR anaphylactic:ab,ti OR 'adverse reaction*':ab,ti OR urticaria*:ab,ti OR 'diffuse erythema':ab,ti OR 'facial edema':ab,ti OR angioedema:ab,ti OR bronchospasm:ab,ti OR 'laryngeal edema':ab,ti OR 'anaphylactic shock':ab,ti OR hypotension:ab,ti OR 'pulmonary edema':ab,ti OR 'cardiac arrest':ab,ti OR 'respiratory arrest':ab,ti) AND (acute:ab,ti OR 'after administration':ab,ti OR rapid*:ab,ti OR severe:ab,ti))<br>AND (treatment:ab,ti OR treat:ab,ti OR recommend*:ab,ti))<br>AND [english]/lim AND [1985-2018]/py<br>NOT 'conference abstract':it NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) |

*Literature Seach NIHR*

| Database | Search string |
|---|---|
| PubMed<br><br>1985 – May 2022 | ((((((("Contrast Media"[Majr] OR contrast medi* [ti] OR contrast agent* [ti] OR contrast material* [ti] OR contrast dose [ti] OR contrast doses [ti] OR contrast dosage [ti] OR radiocontrast medi* [ti] OR radiocontrast agent* [ti] OR radiopaque medi* [ti] OR radiocontrast dose [ti] OR radiocontrast doses [ti] OR radiocontrast dosage [ti] OR "Barium"[Mesh] OR barium [tiab] OR gadolinium [tiab] OR microbubble* [tiab])))<br>AND ((("Drug Hypersensitivity"[Mesh] OR hypersensitiv* [tiab] OR allerg* [tiab] OR anaphylax* [tiab] OR anaphylact* [tiab] OR "Exanthema"[Mesh] OR exanthem* [tiab] OR rash [tiab] OR adverse reaction*[tiab] OR urticaria* [tiab] OR erythem* [tiab] OR hypotension [tiab] OR hypertension [tiab] OR "Stevens-Johnson Syndrome"[Mesh] OR stevens johnson syndrome [tiab] OR sjs [tiab] OR toxic epidermal necrolys* [tiab] OR "Drug Hypersensitivity Syndrome"[Mesh] OR dress syndrome [tiab] OR iodide mump* [tiab]) AND (late [tiab] OR delayed [tiab] OR nonimmediate [tiab])) OR late reaction* [tiab] OR delayed reaction* [tiab] OR nonimmediate reaction* [tiab])))<br>AND (("english"[Language]) AND ("1985"[Date - Publication] : "3000"[Date - Publication])) |
| Embase (Elsevier) | (('contrast medium'/exp/mj OR (((contrast OR radiocontrast) NEAR/2 (medi* OR agent* OR material* OR dose OR doses OR dosage)):ti) OR 'radiopaque medi*':ab,ti OR 'barium'/exp/mj OR barium:ab,ti OR 'gadolinium'/exp/mj OR gadolinium:ab,ti OR 'microbubble'/exp/mj OR microbubble*:ab,ti)<br><br>AND (('hypersensitivity'/exp OR hypersensitiv*:ab,ti OR anaphylax*:ab,ti OR allerg*:ab,ti OR 'rash'/exp OR rash:ab,ti OR 'adverse reaction*':ab,ti OR hypotension:ab,ti OR hypertension:ab,ti OR urticaria*:ab,ti OR erythem*:ab,ti OR exanthem*:ab,ti OR 'stevens johnson syndrome'/exp OR 'stevens johnson syndrome':ab,ti OR sjs:ab,ti OR 'toxic epidermal necrolysis'/exp OR 'toxic epidermal necrolys*':ab,ti OR 'dress syndrome'/exp OR 'dress syndrome':ab,ti OR 'iodide mump*':ab,ti) AND (late:ab,ti OR delayed:ab,ti OR nonimmediate:ab,ti) OR (((late OR delayed OR nonimmediate) NEAR/2 reaction*):ab,ti)))<br><br>AND [english]/lim AND [1985-2022]/py<br>NOT 'conference abstract':it NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) |

**Online Supplement 2**
Relevant studies with risk factor analyses for hypersensitivity and adverse drug reactions to iodine-based contrast media (sorted by year)

| ***Author, Year Type of Reactions*** | ***Origin*** | ***Route of CM Administration*** | ***Cases*** | ***Controls*** | ***Risk Factor*** | ***Frequency (%) / Odds Ratio (adj)*** |
|---|---|---|---|---|---|---|
| **Hypersensitivity Reactions** | | | | | | |
| Fukushima, 2023<br>*Severe IHR* | R | IV<br>(CT) | 45 (0,16%)<br>*4 premedication* | No controls | Iomeprol vs Iopamidol | OR 6,8 |
| McDonald, 2023<br>*All HR* | R | IV<br>(CT) | 1,150 (0,32%) | No controls | Age < 50 years (highest 21-30 years) | OR 1,68-2,26 |
| | | | | | Female sex | OR 1,49 |
| | | | | | Non-white race | OR 1,77 |
| | | | | | Prior HR to ICM | OR 27,6 |
| | | | | | Prior HR to GBCA | OR 1,91 |
| | | | | | Asthma (only moderate-severe HR) | OR 1,45 |
| | | | | | History of other allergies | OR 1,21 |
| | | | | | Iopromide vs Iohexol | OR 3,07 |
| | | | | | Increasing ICM dose | OR 1,30 |
| Voltolini, 2022<br>*All HR* | A | Data not included | 407<br>*400 skin tests*<br>*78 premedication* | 152 | First ICM exposure | OR 2,84 |
| | | | | | Cardiovascular diseases | OR 2,06 |
| | | | | | History of respiratory allergy | OR 2,30 |
| | | | | | History of adverse drug reaction | OR 1,99 |
| Cha, 2019<br>*All HR* | R | Data not included | 1,433 (0,73%)<br>*541 premedication* | 1,433 | Iomeprol | 0,95% |
| | | | | | Iobitridol | 0,89% |
| | | | | | Prior HR to ICM | OR 198,8 |
| | | | | | Hyperthyroidism | OR 3,6 |
| | | | | | History of drug allergy | OR 3,5 |
| | | | | | History of other allergic diseases | OR 6,8 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | Family history of HR to ICM | OR 14,0 |
| Lee, 2019<br>*Immediate HR* | A | IV<br>(CT) | 2004 (0,97%) | No controls | Prior HR to ICM | OR 40,69 |
| | | | | | Age below 50 years | OR 2,11 |
| | | | | | Presence of asthma | OR 1,47 |
| | | | | | Female sex | OR 1,29 |
| | | | | | Comorbid allergic disease | 2,6% |
| | | | | | Patients with chronic liver disease | 3,1% |
| | | | | | Patients with cancer | 2,1% |
| | | | | | | |
| **Adverse Drug Reactions** | | | | | | |
| Zeng, 2024<br>*All ADR* | R | IV<br>(CT) | 522 (0,11%)<br>*Acute 469 (0,099%)*<br>*Delayed 53 (0,011%)* | 522 | Season: summer | OR 1,579 |
| | | | | | Season: autumn | OR 1,925 |
| | | | | | Female sex | 0,141% |
| | | | | | Age 21-30 years | 0,241% |
| | | | | | Iopromide 370 mgI/ml (acute ADR) | 0,218% |
| | | | | | Iodixanol 320 mgI/ml (delayed ADR) | 0,039% |
| Chatani, 2023<br>*All ADR*<br>*(First visit only)* | R | Data not included | 163 (0,72%) | No controls | History of asthma | OR 17,4 |
| | | | | | History of drug allergy | OR 2,4 |
| | | | | | Outpatients | OR 2,1 |
| | | | | | Use of premedication | OR 3,7 |
| Kang, 2022<br>*Delayed ADR* | R | IV<br>(CT) | 207 (2,0%) | 7,260 | Female sex | OR 1,51 |
| | | | | | History of drug allergy | OR 4,59 |
| | | | | | History of allergy | OR 2,54 |
| Li, 2017<br>*All ADR* | R | IV<br>(CT) | 506 (0,42%) | No controls | Female sex | 0,46% |
| | | | | | Prior HR to ICM | 7,17% |
| | | | | | Age 20-29 years | 0.74% |
| | | | | | ICM dose > 100ml | 0,60% |
| | | | | | ICM injection speed > 5ml/s | 0,57% |
| | | | | | BMI > 24 | 0,47% |
| | | | | | IOCM use | 0,69% |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | Patients with asthma | 2,04% |
| | | | | | Patients with heart failure | 1,10% |
| | | | | | Patients with gout | 0,70% |
| Kobayashi, 2013<br>*All ADR* | R | IV<br>(CT) | Derivation:<br>409 (2,0%) | No<br>controls | Prior HR to CM | OR 7,1 |
| | | | | | Urticaria | OR 2,7 |
| | | | | | Allergy to other drugs | OR 1,9 |
| | | | | | ICM concentration >70% | OR 1,9 |
| | | | | | Age < 50 years | OR 1,8 |
| | | | | | CM Iodine dose >65g | OR 1,4 |

*Abbreviations:*
*A = Allergology; ADR = adverse drug reactions; BMI = body mass index; CM = Contrast Media; CT = computed tomography; HR = hypersensitivity reactions; GBCA = gadolinium-based contrast agent; ICM = iodine-based contrast medium; IOCM = iso-osmolar contrast medium; IV = intravenous; OR = Odds Ratio; R = Radiology*

## References


### Hypersensitivity Reactions

Fukushima Y, Taketomi-Takahashi A, Suto T, Hirasawa H, Tsushima Y (2023) Clinical features and risk factors of iodinated contrast media (ICM)-induced anaphylaxis. Eur J Radiol 164:110880.

McDonald JS, Larson NB, Schmitz JJ, et al (2023) Acute adverse events after iodinated contrast agent administration of 359,977 injections: a single-center retrospective study. Mayo Clin Proc 98: 1820-1830. DOI: 10.1016/j.mayocp.2023.02.032.

Voltolini S, Cofini V, Murzilli F, et al (2022) Hypersensitivity reactions to iodinate contrast media in Italy: a retrospective study. Characteristics of patients and risk factors. Eur Ann Allergy Clin Immunol 54: 60-67. DOI: 10.23822/EurAnnACI.1764-1489.225.

Cha MJ, Kang DY, Lee W, et al (2019) Hypersensitivity reactions to iodinated contrast media: a multicenter study of 196,081 patients. Radiology 293: 117-124. DOI: 10.1148/radiol.2019190485.

Lee SY, Kang DY, Kim JY, et al (2019) Incidence and risk factors of immediate hypersensitivity reactions associated with low-osmolar iodinated contrast media: a longitudinal study based on a real-time monitoring system. J Investig Allergol Clin Immunol 29: 444-450. DOI 10.18176/jiaci.0374.

### Adverse Drug Reactions

Zeng W, Tang J, Xu X, et al (2024) Safety of non-ionic contrast media in CT examinations for out-patients: retrospective multicenter analysis of 473,482 patients. Eur Radiol 34: 5570-5577. DOI: 10.1007/s00330-024-10654-2.

Chatani R, Kondo S, Kamimura T, et al (2023) Exploring factors affecting the occurrence of hypersensitivity reactions induced by nonionic iodine contrast media. J Clin Pharmacol 63: 1002-1008. DOI: 10.1002/jcph.2256.

Kang DY, Lee SY, Ahn YH, et al (2022) Incidence and risk factors of late adverse reactions to low-osmolar contrast media: A prospective observational study of 10,540 exposures. Eur J Radiol 146: 110101. DOI: 10.1016/j.ejrad.2021.110101.

Li X, Liu H, Zhao L, et al (2017) Clinical observation of adverse drug reactions to non-ionic iodinated contrast media in population with underlying diseases and risk factors. Br J Radiol 90(1070): 20160729. DOI: 10.1259/bjr.20160729.

Kobayashi D, Takahashi O, Ueda T, Deshpande GA, Arioka H, Fukui T (2013) Risk factors for adverse reactions from contrast agents for computed tomography. BMC Med Inform Decis Mak 13: 18. DOI: 10.1186/1472-6947-13-18.

**Online Supplement 3**
Relevant studies with risk factor analyses for hypersensitivity and adverse drug reactions to gadolinium-based contrast agents (sorted by year)

| ***Author, Year Type of Reactions*** | ***Origin*** | ***Route of CM Administration*** | ***Cases*** | ***Controls*** | ***Risk Factor*** | ***Frequency (%) / Odds Ratio (adj)*** |
|---|---|---|---|---|---|---|
| | | | | | | |
| **Hypersensitivity Reactions** | | | | | | |
| Fukushima, 2024<br>*Immediate HR* | R | IV<br>(MRI) | First 67 (0,16%)<br>Repeat 8 (1,9%)<br>240 of previous HR with premedication | No controls | Gadoxetate | OR 8,03 |
| | | | | | Gadoteridol | OR 4,93 |
| | | | | | Gadopentetate | OR 3,27 |
| | | | | | Younger age | OR 0,99 |
| | | | | | Previous HR to GBCA | 1,9% |
| | | | | | Gadobutrol (repeat HR) | 6,4% |
| Ahn, 2022<br>*All HR* | R | IV<br>(MRI) | 1,304 (0,4%) | No controls | Prior HR to ICM | OR 4,6 |
| | | | | | Gadoteridol | 0,8% |
| McDonald, 2019<br>*All HR* | R | IV<br>(MRI) | 442 (0,16%) | No controls | Gadobenate | OR 3,9 |
| | | | | | Gadobutrol | OR 2,3 |
| | | | | | Female sex | OR 1,7 |
| | | | | | Age 21-50 years | OR 1,4-1,6 |
| | | | | | Outpatients | OR 1,9 |
| | | | | | Abdomen-Pelvis or Prostate MRI | OR 1,4 |
| | | | | | Chest or Cardiac MRI | OR 1,5 |
| Jung, 2012<br>*Immediate HR* | R | IV<br>(MRI) | 112 (0,08%) | No controls | Gadobenate | OR 3,00 |
| | | | | | Female sex | OR 1,69 |
| | | | | | History of allergies/asthma | OR 2,83 |
| | | | | | Recurrence after prior HR | 30% |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Adverse Drug Reactions** | | | | | | |
| Granata, 2016<br>*Immediate ADR* | R | IV<br>(MRI) | 32 (0,30%)<br>1785 with premedication | No controls | Gadobenate | 0,50% |
| Aran, 2015<br>*All ADR* | R | IV<br>(MRI) | 204 (0,1%) | No controls | Gadofosveset meglumine | 0,8% |
| | | | | | Gadoxetate disodium | 0,31% |
| | | | | | Gadobenate | 0,22% |
| | | | | | Female sex | 0,13% |
| | | | | | Outpatients | 0,17% |
| | | | | | Abdomen-Pelvis or Liver MRI | 0,17% |
| Bruder, 2015<br>*Acute ADR* | R | IV<br>(MRI) | 45 (0,12%) | No controls | Gadobenate | 0,42% |
| | | | | | MRI for viability in CAD | 0,22% |
| Nelson, 1995<br>*All ADR* | R | IV<br>(MRI) | 372 (2,4%) | No controls | History of allergies/asthma | 3,7% |
| | | | | | Previous HR to GBCA | 21,3% |
| | | | | | Previous HR to ICM | 6,3% |

*Abbreviations:*
*ADR = adverse drug reactions; CAD = coronary artery disease; GBCA = gadolinium-based contrast agent; HR = hypersensitivity reactions; ICM = iodine-based contrast medium; IV = intravenous; MRI = magnetic resonance imaging; OR = Odds Ratio; R = Radiology*

**References**

Fukushima Y, Ozaki D, Taketomi-Takahashi A, et al (2024) Assessment of first-time and repeated acute adverse reactions to gadolinium-based contrast agents in MRI: A retrospective study. Eur J Radiol 176: 111504. DOI: 10.1016/j.ejrad.2024.111504.

Ahn YH, Kang DY, Park SB, et al (2022) Allergic-like hypersensitivity reactions to gadolinium-based contrast agents: An 8-year cohort study of 154,539 patients. Radiology 303: 329-336. DOI: 10.1148/radiol.210545.

McDonald JS, Hunt CH, Kolbe AB, et al (2019) Acute adverse events following gadolinium-based contrast agent administration: A single-center retrospective study of 281,945 injections. Radiology 292: 620-627. DOI: 10.1148/radiol.2019182834.

Jung JW, Kang HR, Kim MH, et al (2012) Immediate hypersensitivity reaction to gadolinium-based MR contrast media. Radiology 264: 414-422. DOI: 10.1148/radiol.12112025.

Granata V, Cascella M, Fusco R, et al (2016) Immediate adverse reactions to gadolinium-based MR contrast media: A retrospective analysis on 10,608 examinations. Biomed Res Int 2016: 3918292. DOI: 10.1155/2016/3918292.

Aran S, Shaqdan KW, Abujudeh HH (2015) Adverse allergic reactions to linear ionic gadolinium-based contrast agents: Experience with 194,400 injections. Clin Radiol 70: 466-475. DOI: 10.1016/j.crad.2014.12.011.

Bruder O, Schneider S, Pilz G, et al (2015) 2015 Update on acute adverse reactions to gadolinium-based contrast agents in cardiovascular MR. Large multi-national and multi-ethnical population experience with 37788 patients from the EuroCMR Registry. J Cardiovasc Magn Reson 17: 58. DOI: 10.1186/s12968-015-0168-3.

Nelson KL, Gifford LM, Lauber-Huber C, Gross CA, Lasser TA (1995) Clinical safety of gadopentetate dimeglumine. Radiology 196: 439-443.

**Online Supplement 4:**

## EXAMPLE OF A LETTER FOR THE PATIENT TO TAKE TO THE ALLERGY CONSULTATION

Dear Colleague,

(Insert patient's name and details) had a hypersensitivity reaction after the administration of a contrast agent on (insert location and date).

Examination type (e.g., Angiography, CT, MRI, US, Fluoroscopy):

Type of contrast agent:

- Iodine-based
- Gadolinium-based
- Ultrasound

Name of the specific contrast agent:

Concentration:

Volume administered: (xxx) ml

Route of administration (e.g., IV, IA, intra-articular, oral, rectal, local.....):

Time between the injection and the start of the clinical symptoms:

Type of symptoms and their evolution (describe):

**Modified Ring-Messmer classification of systemic reactions**

| Grade | Skin | Abdomen | Airways | Cardiovascular |
|---|---|---|---|---|
| I | Itch<br>Flush<br>Urticaria<br>Angioedema | - | - | - |
| II | Itch<br>Flush<br>Urticaria<br>Angioedema | Nausea<br>Cramps | Rhinorrhoea<br>Hoarseness<br>Dyspnoea | Tachycardia (>20 bpm rise)<br>Hypotension (>20 mm Hg drop in systolic blood pressure)<br>Arrhythmia |
| III | Itch<br>Flush<br>Urticaria<br>Angioedema | Vomiting<br>Defecation | Laryngeal oedema<br>Bronchospasm<br>Cyanosis | Shock |
| IV | Itch<br>Flush<br>Urticaria<br>Angioedema | Vomiting<br>Defecation | Respiratory arrest | Cardiac arrest |
| *Classification according to the most severe symptom, no symptom is mandatory* | | | | |

Treatment given during the reaction: • (please specify)

Outcome (e.g., follow up, return home, hospital admission, ICU,.....):

Tryptase performed at the time of the reaction: Yes/No
Tryptase performed 2h after start of the reaction: Yes/No
Results: ug/ml

Previous history of contrast agent reaction: Yes/No

If yes, please specify location, date, name and type of contrast agent and symptoms:

Thank you for seeing the patient and performing an allergic study to categorize the reaction as either allergic or non-allergic hypersensitivity, and to look for cross-reactivity so that a safer contrast agent can be recommended for future injections.

Yours sincerely,

Dr (Name and details)