Guideline Safe Use of Contrast Media Part 2

This part comprises:

1. **Hypersensitivity reactions after contrast media administration**
2. **Safe use of gadolinium-containing contrast media**
3. **Safe injection of contrast media through central catheters and ports**
4. **Contrast media extravasation**

INITIATED BY
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The Dutch Society of Allergology and Clinical Immunology
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Colophon
GUIDELINE SAFE USE OF CONTRAST MEDIA - PART 2

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Summary of Recommendations

Summary of recommendations of Hypersensitivity Reactions to CM

Module 1: Clinical question
What is the optimal treatment for acute hypersensitivity reactions after administration of contrast media?

Recommendations

Preparation:
- Have the drugs (as a minimum requirement: adrenaline, salbutamol, H1-antihistamine (clemastine) IV, and corticosteroid IV (for example prednisolone)), equipment and protocol for treatment of an acute adverse reaction readily available in every room where contrast agents are administered.
- Adhere to local protocols for accessibility of a resuscitation and emergency response team.
- Keep every patient with an acute hypersensitivity reaction to CM in a medical environment for at least 30 minutes after contrast agent injection. Moderate and severe reactions need a prolonged observation.

Acute management general principles:
- Check and stabilize patient according to the ABCDE method.
- Stop infusing contrast agent and replace IV line with crystalloid.
- Dyspnoea or stridor: let patient sit up.
- Hypotension: keep patient in prone position, raise legs.
- Consider measuring serum tryptase (see recommendations in chapter Laboratory Diagnosis of Hypersensitivity Reactions to Contrast Media).
- Record acute allergic reactions in allergy registry (see chapter Organization of Healthcare).

Note: After administration of clemastine the patient may no longer be able (or insured) to drive a car/motorcycle or to operate machinery.

Severe reactions:
Cardiac or respiratory arrest:
- Start CPR.
- Call the CPR team.

Anaphylactic reaction or stridor:
- Call rapid response team (SIT-team).
- Give oxygen 10 to 15 L/min with non-rebreathing mask.
- Give 0.5mg adrenaline IM in lateral upper thigh.
- Give fluid bolus of crystalloid 500ml IV in 10 minutes, repeat as necessary.
- Consider nebulizing with salbutamol 5mg or budesonide 2mg for stridor.
- Give clemastine 2mg IV, repeat as necessary.
- Consider adding corticosteroid (for example prednisolone 50mg IV*).

*Or equivalent dose of other corticosteroid
50 mg prednisolone is equivalent to:
- 40 mg methylprednisolone.
- 8mg dexamethasone.
- 200mg hydrocortisone.

*Consider adding corticosteroids to prevent protracted or biphasic anaphylactic reactions if initial symptoms are severe.

Moderate reactions:
Consider transferring the patient to a department with facilities for monitoring of vital functions.

Isolated bronchospasm:
- Salbutamol 2.5 to 5mg nebulization in oxygen by facemask 10 to 15 L/min (nebulization is easier to administer and more effective than dose aerosol).
- In mild cases asthma patients may use their own salbutamol dose aerosol.
- In case of deterioration give adrenaline 0.5mg IM and consider call rapid response team.

Isolated facial oedema without stridor:
- Give oxygen 10 to 15L/min via anon-rebreathing mask.
- Give clemastine 2mg IV.
- If oedema is severe or near airways or if stridor develops: treat as anaphylaxis.

Isolated urticaria/diffuse erythema:
- Give clemastine 2mg IV.
- If accompanied by hypotension: treat as anaphylaxis.

Isolated hypotension:
- Give bolus of crystalloid 500ml IV, repeat as necessary.
- If accompanied by bradycardia, consider atropine 0.5mg IV.
- If accompanied by other symptoms: treat as anaphylaxis.

Mild reactions:

General:
- Mild reactions may only need reassurance.
- Observe vital signs until symptoms resolve.
- Do not remove iv access during observation.

Consider:
- Prescribing a non-sedating antihistamine, for example desloratadine 5mg PO (once daily) for mild allergic reactions.
- Ondansetron 4mg IV for protracted vomiting.

Module 2: Clinical question
What is the optimal treatment for late hypersensitivity reactions to contrast media?

Recommendations

Warn patients who have had a previous hypersensitivity reaction to contrast media, that a late hypersensitivity reaction may be possible, usually a skin reaction.

Patients should contact their general practitioner if they have a late hypersensitivity reaction after CM administration.

Consider informing the radiology department where the CM was administered about the occurrence and symptoms of a late hypersensitivity reaction after CM administration.

When the symptoms of a late hypersensitivity reaction are mild, a wait-and-see approach can be justified.

Treat late hypersensitivity reactions symptomatically.
Consider treatment of skin reactions with oral or topical corticosteroids.

When severe symptoms develop, such as generalized pustulosis or painful cutaneous blisters, refer the patient to a dermatologist.

Module 3: Clinical question
What is the diagnostic value of laboratory testing for hypersensitivity reactions to contrast media?

Recommendations

Do not perform a Basophil Activation Test routinely in all patients with a history of hypersensitivity reactions receiving contrast medium.

Measure serum tryptase between 1 to 2 hours from the start of all moderately severe to severe acute hypersensitivity reactions to contrast media.

When tryptase is elevated, refer the patient to a drug allergy specialist.

Module 4: Clinical question
What is the diagnostic value of skin testing for hypersensitivity reactions to contrast media?

Recommendations

Do not perform skin tests routinely after every hypersensitivity reaction to a contrast medium.

Refer the patient to a specialist in drug allergy to perform skin tests within 6 months after the hypersensitivity reaction in the following patient groups:
- Severe hypersensitivity reactions to a contrast medium.
- Hypersensitivity reactions with increased tryptase levels.
- Hypersensitivity reactions to 2 or more different contrast media of the same type (for example 2 different iodine-based CM) or to 2 or more types of contrast media (for example iodine-based CM and gadolinium-based CA).

Always specify the used contrast agent in the referral.

Refer the patient to a specialist in drug allergy to perform skin tests in all patients with breakthrough hypersensitivity reactions despite premedication with corticosteroids and H1-antihistamines.

Module 5: Clinical question
Which prophylactic measures should be taken in patients with increased risk of hypersensitivity reactions after contrast administration?

Recommendations (See also Flowcharts 1- 4)

I Patients with a previous (acute) hypersensitivity reaction to a **known ICM or GBCA**

A Elective (plannable) examinations with ICM or GBCA

In all patients with a (documented) history of a hypersensitivity reaction to an iodine-based or gadolinium-based CM, consider an alternative imaging modality. When this is not possible, consider performing unenhanced exam, if this has an acceptable reduction in

diagnostic quality.

If the previous hypersensitivity reaction was mild:
- Choose a different ICM or GBCA*.
- Observe the patient ≥ 30 min with IV in place.
- Be vigilant to react to a possible new hypersensitivity reaction.

If the previous hypersensitivity reaction was moderate:
- Choose a different ICM or GBCA*.
- Observe the patient ≥ 30 min with IV in place.
- Be vigilant to react to a possible new hypersensitivity reaction.

In cases of doubtful severity consider referring the patient to a drug allergy specialist for allegologic skin testing with a panel of different iodine-based or gadolinium-based CM.

If the previous hypersensitivity reaction was severe:
- If clinically reasonable, defer the imaging study until results of allergologic skin testing are available.
- Refer the patient to a drug allergy specialist for allegologic skin testing with a panel of different iodine-based or gadolinium-based CM.
- Apply the advice of the drug allergy specialist with regard to choice of alternative CM and use of premedication in future examinations.
- If no or positive advice for premedication: Premedicate with 2 x 25 mg prednisolone PO/IV** 12h and 2h before CM administration and 2mg clemastine IV within 1h before CM administration.
- Observe the patient ≥ 30 min with IV in place.
- Be vigilant to react to a possible new hypersensitivity reaction.

B Acute (within hours) or emergency (direct) examinations with ICM or GBCA

In all patients with a (documented) history of a hypersensitivity reaction to an iodine-based CM, consider an alternative imaging modality. When this is not possible, consider performing unenhanced exam, if this has an acceptable reduction in diagnostic quality.

If the previous hypersensitivity reaction was mild:
- Choose a different ICM or GBCA*.
- Observe the patient ≥ 30 min with IV in place.
- Be vigilant to react to a possible new hypersensitivity reaction.

If the previous hypersensitivity reaction was moderate:
- Premedicate with 50 mg prednisolone IV** and 2 mg clemastine IV within 30min before CM administration.
- Choose a different ICM or GBCA*.
- Observe the patient ≥ 30 min with IV in place.
- Be vigilant to react to a possible new hypersensitivity reaction.

If the previous hypersensitivity reaction was severe:
- Premedicate with 50 mg prednisolone IV** and 2mg clemastine IV within 30min before CM administration
- Choose a different ICM or GBCA*.
- Observe the patient ≥ 30 min with IV in place.

- Be vigilant to react to a possible new hypersensitivity reaction.

II Patients with a previous (acute) hypersensitivity reaction to an **unknown ICM or GBCA**

A Elective (plannable) examinations with ICM or GBCA

In all patients with a (documented) history of a hypersensitivity reaction to an iodine-based or gadolinium-based CM, consider an alternative imaging modality. When this is not possible, consider performing unenhanced exam, if this has an acceptable reduction in diagnostic quality.

If the previous hypersensitivity reaction was mild:
- Proceed with the radiologic examination normally.
- Observe the patient ≥ 30 min with IV in place.
- Be vigilant to react to a possible new hypersensitivity reaction.

If the previous hypersensitivity reaction was moderate:
- Proceed with the radiologic examination normally.
- Observe the patient ≥ 30 min with IV in place.
- Be vigilant to react to a possible new hypersensitivity reaction.

In cases of doubtful severity consider referring the patient to a drug allergy specialist for allergologic skin testing with a panel of different iodine-based or gadolinium-based CM.

If the previous hypersensitivity reaction was severe:
- If clinically reasonable, defer the imaging study until results of allergologic skin testing are available.
- Refer the patient to a drug allergy specialist for allergologic skin testing with a panel of different iodine-based or gadolinium-based CM.
- Apply the advice of the drug allergy specialist with regard to choice of possible CM and use of premedication in future examinations.
- If no or positive advice for premedication: Premedicate with 2 x 25 mg prednisolone PO/IV** 12h and 2h before CM administration and 2mg clemastine IV within 1h before CM administration.
- Observe the patient ≥ 30 min with IV in place.
- Be vigilant to react to a possible new hypersensitivity reaction.

B Acute (within hours) or emergency (direct) examinations with ICM or GBCA

In all patients with a (documented) history of a hypersensitivity reaction to an iodine-based or gadolinium-based CM, consider an alternative imaging modality. When this is not possible, consider performing unenhanced exam, if this has an acceptable reduction in diagnostic quality.

If the previous hypersensitivity reaction was mild:
- Proceed with the radiologic examination normally.
- Observe the patient ≥ 30 min with IV in place.
- Be vigilant to react to a possible new hypersensitivity reaction.

If the previous hypersensitivity reaction was moderate:
- Premedicate with 50 mg prednisolone IV** and 2mg clemastine IV within 30min before CM administration.

- Proceed with the radiologic examination normally.
- Observe the patient ≥ 30 min with IV in place.
- Be vigilant to react to a possible new hypersensitivity reaction.

If the previous hypersensitivity reaction was severe:
- Premedicate with 50 mg prednisolone IV** and 2mg clemastine IV within 30min before CM administration.
- Proceed with the radiologic examination normally.
- Observe the patient ≥ 30 min with IV in place.
- Be vigilant to react to a possible new hypersensitivity reaction.

III Patients with previous breakthrough reactions to ICM or GBCA

In patients with breakthrough hypersensitivity reactions to iodine-based or gadolinium-based CM apply the same as above, but always refer the patient to a drug allergy specialist for allergologic skin testing with a panel of different ICM or GBCA.

IV Patients with previous hypersensitivity reactions to multiple CM

In patients with hypersensitivity reactions to multiple iodine-based or gadolinium-based CM (either 2 or more different iodine-based CM or gadolinium-based CA or to an iodine-based CM and a gadolinium-based CA) apply the same as above, but always refer the patient to a drug allergy specialist for allergologic skin testing with a panel of different ICM and GBCA.

V Patients with previous non-severe late hypersensitivity reactions to ICM or GBCA

In patients with previous mild or moderate late hypersensitivity reactions to iodine-based CM or gadolinium-based CA premedication is not recommended, even in acute or emergency examinations.

Notes:

* Consider cross-reactivity of iodine-based CM (see Introduction to this section, table 2).

**Or equivalent dose of another glucocorticosteroid
25 mg or 50 mg prednisolone is equivalent to:
- 20 mg or 40 mg methylprednisolone.
- 4 mg or 8 mg dexamethasone.
- 100 mg or 200mg hydrocortisone

Recommendations for hypersensitivity reactions after non-vascular CM administration

Small amounts of ICM or GBCA can be absorbed by mucosa and enter the systemic circulation after all types of nonvascular CM administration.

Hypersensitivity reactions after nonvascular administration of ICM and GBCA can occur, but their incidence is low to very low.

No preventive measures are indicated for ERCP or for nonvascular GBCA administration.

For other indications using ICM no firm recommendations can be given for patients that

have experienced hypersensitivity reactions to CM in the past.

In patients that have experienced *severe* hypersensitivity reactions to CM in the past, alternative imaging or contrast agents should be explored with the radiologist, and a strict indication for examinations using nonvascular CM administration is needed.

In patients that have experienced *severe* hypersensitivity reactions to CM in the past, preventive measures for severe reactions as outlined in Module 5 may be followed prior to examinations using nonvascular CM administration, if possible after laboratory and skin testing by a specialist in drug allergy prior to the examination.

Summary of Recommendations for GBCA-enhanced Imaging

Module 6: Clinical Question
How can PC-AKI be prevented in administration of Gadolinium-Based (Gd) Contrast Agents (GBCA)?

Recommendations

Use optimal CM dosing based on patient weight in local dosing protocols for diagnostic MRI examinations.

Do not use prophylactic measures to avoid the development of PC-AKI in high-risk patients (eGFR<30ml/min/1.73m^2) receiving GBCA intravenously at the appropriate dose.

Do not substitute ICM with GBCA in order to avoid PC-AKI in computed tomography and/or digital subtraction angiography.

Module 7: Clinical Question
a) Which patients are at-risk for Nephrogenic Systemic Fibrosis (NSF)?
b) Which measures are necessary to prevent Nephrogenic Systemic Fibrosis?

Recommendations

Use low-risk (ionic and non-ionic) **macrocyclic** GBCAs for medical imaging in all patients. Linear GBCAs have been associated with NSF, therefore, consider **linear** agents only if a macrocyclic agents cannot answer the diagnostic question.

Make an individual risk-benefit analysis with the patient's requesting physician and nephrologist to ensure a strict indication for gadolinium-enhanced MRI using **linear** agents in patients with eGFR < 30 ml/min/1.73m^2.

For prevention of NSF in patients who are already dependent on haemodialysis or peritoneal dialysis, the administration of **macrocyclic** GBCA does not have to be followed by an immediate haemodialysis session.

To limit the amount of circulating GBCA, in hemodialysis patients the administration of **linear** GBCA should be followed immediately by a (high-flux) haemodialysis session, which is repeated on the following two days.

In predialysis patients (eGFR<15 ml/min/1.73m^2) and peritoneal dialysis patients, the risk of NSF due to **linear** GBCA should be weighed against the risk of placement of a temporary

haemodialysis catheter.

Module 8: Clinical Question

What is the clinical relevance of gadolinium-based contrast agent (GBCA) induced T1w hyperintensity of the nucleus dentatus and the globus pallidus in the brain?

Recommendations

Ensure a strict indication for gadolinium-enhanced MRI and use EMA-approved GBCA in all patients to minimize possible gadolinium deposition.

Summary of recommendations for other topics

Module 9: Clinical question

How can central venous catheters (CVC), haemodialysis catheters (HC), peripherally inserted central catheters (PICC), and totally implantable venous access devices (TIVAD) be safely used for the administration of intravenous contrast agents, particularly using power injectors and higher injection rates for obtaining high-quality images?

Recommendations

Note: High quality of imaging is generally needed for low-contrast situations, such as in staging studies in brain, head & neck, hepatobiliary, genitourinary or colorectal imaging.
Lower quality may be acceptable for high-contrast situations such as in follow-up studies of lymph nodes (lymphoma, testicular cancer) or in pulmonary or musculoskeletal imaging.

Use a power injector and a peripheral venous access catheter for IV contrast media administration to obtain the best level of quality of contrast-enhanced imaging, especially in low-contrast situations (see Note).

When a peripheral venous catheter is unavailable: Check the position of the CVC, TIVAD, or PICC line and its patency before and after the power-injected contrast administration.

Power-injectable central venous catheters may be safely used for administration of CM using a power injector, when most recent recommendations of the catheter manufacturer are followed.

Power-injectable haemodialysis catheters may be safely used for administration of CM using a power injector, when most recent recommendations of the catheter manufacturer are followed.

Especially in haemodialysis patients, vein preservation should weigh heavily in the choice of access for CM administration. When the use of a peripheral vein for contrast administration in haemodialysis patients is inevitable, the veins in the elbow fold should be used as much as possible. If this is impossible, veins on the back of the hand or the use of dialysis fistula for contrast administration should be considered in consultation with a nephrologist.

There is a risk of catheter tip migration of PICCs and TIVADs when CM is injected via a power injector in patients with a catheter tip position above the tracheobronchial angle.
When a power-injectable PICC or TIVAD is used for CM administration, check the position of the catheter tip with DX, CT or fluoroscopy before and after power-injection of CM.

When a power-injectable CVC, HC, PICC or TIVAD is used for CM administration with a power injector, check the patency of the catheter after the procedure by manual flush of 20ml normal saline.
When a power-injectable HC is used for CM administration, immediately after power-injection a patient-specific lock solution should be installed by a certified dialysis nurse.

See Appendix 1 for recommendations on flow rates and injection pressures for a large number of commercially available CVCs, HCs, PICCs, and TIVADs in The Netherlands.

Module 10: Clinical question
What is the optimal treatment in contrast media extravasation?

Recommendations

Consider the following treatment options for contrast extravasation:
- Try to aspirate the extravasated contrast medium through an inserted needle.
- Mark affected area.
- Use compresses, for relieving pain at the injection site.
- Use pain killers.
- Elevate the affected extremity above the level of the heart.

Record contrast extravasation and treatment in the patient record (volume, CM concentration, area, clinical findings).

Give the patient clear instructions when to seek additional medical care:
- Any worsening of symptoms.
- Skin ulceration.
- Development of any neurologic or circulatory symptoms, including paraesthesia's.
- Give the patient a patient information leaflet.

For severe extravasation injury:
- Consult a plastic surgeon.
- Notify the referring physician.

Samenvatting van Aanbevelingen in het Nederlands

Samenvatting van aanbevelingen voor Overgevoeligheidsreacties na contrastmiddelen

Module 1: Uitgangsvraag
Wat is de optimale behandeling van acute overgevoeligheidsreacties na toediening van contrast middelen (CM)?

Aanbevelingen

Voorbereiding:
- Zorg ervoor dat de medicatie (als minimum vereiste: adrenaline, salbutamol, H1-antihistaminicum (clemastine) IV en corticosteroid IV (bijvoorbeeld prednisolon)), uitrusting en protocol voor de behandeling van een acute overgevoeligheidsreactie gereed liggen in elke kamer waar contrastmiddelen worden toegediend.
- Houd je aan lokale protocollen voor bereikbaarheid van een reanimatie en een spoed interventie team.
- Houd elke patiënt met een acute overgevoeligheidsreactie na toediening van CM in een medische omgeving gedurende minstens 30 minuten na injectie van CM. Matige en ernstige reacties behoeven een langere observatietijd.

Acute management, algemene principes:
- Check and stabiliseer de patiënt volgens de ABCDE-methode.
- Stop met toediening van CM en vervang infuus door een kristalloïd.
- Dyspneu of stridor: laat patient rechtop zitten.
- Hypotensie: houd patiënt in liggende positie, leg de benen hoger.
- Overweeg het bepalen van serum tryptase (zie aanbevelingen in module Laboratory Diagnosis of Hypersensitivity Reactions to Contrast Media).
- Vermeld acute overgevoeligheidsreacties in de allergie registratie van het Elektronisch Patiënten Dossier (zie module Organisation of Healthcare).

N.B: Na toediening van clemastine kan het reactievermogen van de patiënt sterk verminderd zijn. Patiënt wordt afgeraden gedurende die tijd een voertuig te besturen of een machine te bedienen Patiënt is strafbaar en vaak niet verzekerd bij eventueel ongeluk/ schade.

Ernstige reacties:
Cardiaal of respiratoir arrest:
- Start cardiopulmonale reanimatie.
- Bel het reanimatie team.

Anafylactische reactie of stridor:
- Bel het Spoed Interventie Team (SIT-team).
- Geef zuurstof 10 tot 15L/min via een non-rebreathing masker.
- Geef 0.5mg adrenaline IM in laterale bovenste deel van het dijbeen.
- Geef bolus van een kristalloïd 500ml IV in 10 minuten, herhaal indien nodig.
- Overweeg verneveling met salbutamol 5mg of budesonide 2mg voor stridor.
- Geef clemastine 2mg IV, herhaal indien nodig.
- Overweeg toevoegen corticosteroid (b.v. prednisolon 50mg IV*)

* Of equivalente dosis van een ander corticosteroid
50 mg prednisolon is equivalent aan:
- 40 mg methylprednisolone.
- 8mg dexamethasone.

- 200mg hydrocortisone.

* Overweeg toevoegen van corticosteroiden voor preventie van geprotraheerde of bifasische anafylactische reacties als de initiële symptomen ernstig zijn.

Matig-ernstige reacties:
Overweeg om patiënt te verplaatsen naar een afdeling met faciliteiten voor het monitoren van vitale functies.

Geïsoleerd bronchospasme:
- Salbutamol 2.5 tot 5mg verneveling in zuurstof door middel van een gezichtsmasker 10 tot 15 L/min (verneveling is makkelijker om toe te dienen en meer effectief dan dosis aerosol).
- Bij milde reacties mogen astma patiënten de eigen salbutamol dosis aerosol gebruiken.
- Indien klachten toenemen geef adrenaline 0.5mg IM en neem contact op met het spoed interventie team.

Geïsoleerd gezichtsoedeem zonder stridor:
- Geef zuurstof 10 tot 15L/min via een non-rebreathing masker.
- Geef clemastine 2mg IV.
- Indien oedeem ernstig is of dichtbij luchtwegen is gelokaliseerd of indien er stridor ontstaat: behandel als anafylaxie.

Geïsoleerde urticaria/diffuse erytheem:
- Geef clemastine 2mg IV.
- Indien vergezeld van hypotensie: behandel als anafylaxie.

Geïsoleerde hypotensie:
- Geef bolus van kristalloïd 500ml IV, herhaal indien nodig.
- Indien vergezeld van bradycardie, overweeg atropine 0.5mg IV.
- Indien vergezeld door andere symptomen behandel als anafylaxie.

Milde reacties

Algemeen:
- Milde reacties behoeven soms enkel geruststelling.
- Observeer vitale functies totdat symptomen voorbij zijn.
- Verwijder iv toegang niet tijdens observatie.

Overweeg:
- Voorschrijven van een niet-sederend H1-antihistaminicum, bijvoorbeeld desloratidine 5mg PO (eenmaal daags) voor milde overgevoeligheidsreacties.
- Ondansetron 4mg iv voor persistent overgeven.

Module 2: Uitgangsvraag
Wat is de optimale behandeling van late overgevoeligheidsreacties na toediening van CM?

Aanbevelingen

Waarschuw patiënten die eerder een overgevoeligheidsreactie hebben gehad na CM, dat een late overgevoeligheidsreactie mogelijk is, meestal een huidreactie.

Patiënten moeten contact opnemen met hun huisarts als zij een late overgevoeligheids reactie hebben na CM toediening.

Overweeg om de afdeling Radiologie waar het CM werd toegediend te informeren over het optreden en de symptomen van een late overgevoeligheidsreactie na CM toediening.

Wanneer de symptomen van een late overgevoeligheidsreactie mild zijn is afwachten te verdedigen.

Behandel late overgevoeligheidsreacties naar gelang de symptomen.
Overweeg behandeling van huidreacties met orale of topicale corticosteroiden.

Wanneer ernstige symptomen ontstaan, zoals gegeneraliseerde pustulosis of pijnlijke cutane blaren, verwijs dan de patiënt naar een dermatoloog.

Module 3: Uitgangsvraag
Wat is de diagnostische waarde van laboratorium testen voor overgevoeligheidsreacties na toediening van CM?

Aanbevelingen

Voer een Basofielen Activatie Test niet routinematig uit bij alle patiënten met een voorgeschiedenis van overgevoeligheidsreacties na toediening van CM.

Meet serum tryptase tussen 1 tot 2 uren na aanvang van alle matige-ernstige tot ernstige overgevoeligheidsreacties na toediening van CM.

Verwijs de patiënt naar een specialist in geneesmiddelenovergevoeligheid indien de tryptase verhoogd is.

Module 4: Uitgangsvraag
Wat is de diagnostische waarde van huidtesten voor overgevoeligheidsreacties na toediening van CM?

Aanbevelingen

Voer huidtesten niet routinematig uit bij elke overgevoeligheidsreactie na toediening van CM.

Verwijs de patiënt naar een specialist in geneesmiddelenovergevoeligheid voor het uitvoeren van huidtesten binnen 6 maanden bij patiënten die het volgende hebben gehad:

- Ernstige overgevoeligheidsreacties na toediening van CM.
- Overgevoeligheidsreacties met verhoogde tryptase.
- Overgevoeligheidsreacties na twee of meer verschillende CM van hetzelfde type (bijvoorbeeld twee jodiumhoudende CM) of verschillende types (bijvoorbeeld een jodiumhoudend en een gadolinium houdend CM).

Specificeer het gebruikte contrastmiddel in de verwijzing.

Verwijs de patiënt naar een geneesmiddelenallergie specialist voor het uitvoeren van huidtesten in alle gevallen van doorbraak overgevoeligheidsreacties ondanks premedicatie met corticosteroiden en H1-antihistaminica.

Module 5: Uitgangsvraag
Welke profylactische maatregelen moeten worden genomen bij patiënten met een verhoogd risico op overgevoeligheidsreacties na toediening van CM?

Aanbevelingen (Zie ook Flowcharts 1 – 4)

I Patiënten met een eerdere (acute(overgevoeligheidsreactie op een bekend **ICM of GBCA.**

A Electieve (planbare) onderzoeken met ICM of GBCA

Overweeg een alternatieve beeldvormingsmodaliteit bij alle patiënten met een (gedocumenteerde) geschiedenis van een overgevoeligheidsreactie voor een ICM of GBCA, indien mogelijk.

Indien dit niet mogelijk is, overweeg het uitvoeren van het onderzoek zonder contrastmiddel, indien de reductie van diagnostische kwaliteit acceptabel is.

Indien de vorige overgevoeligheidsreactie mild was:
- Kies een ander ICM of GBCA*.
- Observeer de patiënt ≥ 30 minuten met het infuus in.
- Wees waakzaam om te reageren op een mogelijke nieuwe overgevoeligheidsreactie.

Indien de vorige overgevoeligheidsreactie matig-ernstig was:
- Kies een ander ICM of GBCA*.
- Observeer de patiënt ≥ 30 minuten met het infuus in.
- Wees waakzaam om te reageren op een mogelijke nieuwe overgevoeligheidsreactie.

Bij twijfel aan de ernst van de vorige overgevoeligheidsreactie: overweeg om de patiënt te verwijzen naar een specialist in geneesmiddelenovergevoeligheid voor huidtesten met verschillende ICM of GBCA.

Indien de vorige overgevoeligheidsreactie ernstig was:
- Indien mogelijk, stel het beeldvormend onderzoek uit totdat resultaten van huidtesten bekend zijn.
- Verwijs de patiënt naar een specialist in geneesmiddelenovergevoeligheid voor huidtesten met verschillende ICM of GBCA.
- Pas het advies van de specialist in geneesmiddelenovergevoeligheid toe met betrekking tot het kiezen van een alternatief CM en gebruik van premedicatie bij toekomstige onderzoeken.
- Indien positief of geen advies over premedicatie: Geef premedicatie 2 x 25 mg prednisolon PO/IV** 12h en 2h voor CM toediening en 2mg clemastine IV binnen 1h voor CM toediening.
- Observeer de patiënt ≥ 30 min met het infuus in
- Wees waakzaam om te reageren op een mogelijke nieuwe overgevoeligheidsreactie.

B Acuut (binnen enkele uren) of spoed (direct) onderzoek met ICM of GBCA

Overweeg een alternatieve beeldvormingsmodaliteit bij alle patiënten met een (gedocumenteerde) geschiedenis van een overgevoeligheidsreactie voor een ICM of GBCA, indien mogelijk.

Indien dit niet mogelijk is, overweeg het uitvoeren van het onderzoek zonder contrastmiddel, indien de reductie van diagnostische kwaliteit acceptabel is.

Indien de vorige overgevoeligheidsreactie mild was:
- Kies een ander ICM of GBCA*.

- Observeer de patiënt ≥ 30 minuten met het infuus in.
- Wees waakzaam om te reageren op een mogelijke nieuwe overgevoeligheidsreactie.

Indien de vorige overgevoeligheidsreactie matig-ernstig was:
- Geef premedicatIe: 50 mg prednisolon IV** en 2mg clemastine IV binnen 30min voor CM toediening.
- Kies een ander ICM of GBCA*.
- Observeer de patiënt ≥ 30 minuten met het infuus in.
- Wees waakzaam om te reageren op een mogelijke nieuwe overgevoeligheidsreactie.

Indien de vorige overgevoeligheidsreactie ernstig was:
- Geef premedicatIe: 50 mg prednisolon IV** en 2mg clemastine IV binnen 30min voor CM toediening.
- Kies een andere ICM of GBCA*.
- Observeer de patiënt ≥ 30 minuten met het infuus in.
- Wees waakzaam om te reageren op een mogelijke nieuwe overgevoeligheidsreactie.

II Patiënten met een eerdere (acute) overgevoeligheidsreactie na een **onbekend ICM of GBCA**

A Electieve (planbare) onderzoeken met ICM of GBCA

Overweeg een alternatieve beeldvormingsmodaliteit bij alle patiënten met een (gedocumenteerde) geschiedenis van een overgevoeligheidsreactie voor een ICM of GBCA, indien mogelijk.

Indien dit niet mogelijk is, overweeg het uitvoeren van het onderzoek zonder contrastmiddel, indien de reductie van diagnostische kwaliteit acceptabel is.

Indien de vorige overgevoeligheidsreactie mild was:
- Voer het radiologisch onderzoek uit zoals gebruikelijk
- Observeer de patiënt ≥ 30 minuten met het infuus in
- Wees waakzaam om te reageren op een mogelijke nieuwe overgevoeligheidsreactie.

Indien de vorige overgevoeligheidsreactie matig-ernstig was:
- Voer het radiologisch onderzoek uit zoals gebruikelijk
- Observeer de patiënt ≥ 30 minuten met het infuus in.
- Wees waakzaam om te reageren op een mogelijke nieuwe overgevoeligheidsreactie.

Bij twijfel aan de ernst van de vorige overgevoeligheidsreactie: overweeg om de patiënt te verwijzen naar een specialist in geneesmiddelenovergevoeligheid voor huidtesten met verschillende ICM of GBCA.

Indien de vorige overgevoeligheidsreactie ernstig was:
- Indien klinisch mogelijk, stel het beeldvormend onderzoek uit totdat resultaten van huidtesten bekend zijn.
- Verwijs de patiënt naar een specialist in geneesmiddelenovergevoeligheid voor huidtesten met een vaste selectie van verschillende ICM of GBCA.
- Pas het advies van de specialist in geneesmiddelenovergevoeligheid toe met betrekking tot het kiezen van een mogelijk CM en het gebruik van premedicatie bij toekomstige onderzoeken.
- Indien positief of geen advies over premedicatie: Geef premedicatie 2 x 25 mg

prednisolon PO/IV** 12h en 2h voor CM toediening en 2mg clemastine IV binnen 1h voor CM toediening.
- Observeer de patiënt ≥ 30 min met het infuus in
- Wees waakzaam om te reageren op een mogelijke nieuwe overgevoeligheidsreactie.

B Acuut (binnen enkele uren) of spoed (direct) onderzoek met ICM of GBCA

Overweeg een alternatieve beeldvormingsmodaliteit bij alle patiënten met een (gedocumenteerde) geschiedenis van een overgevoeligheidsreactie voor een ICM of GBCA, indien mogelijk.

Indien dit niet mogelijk is, overweeg het uitvoeren van het onderzoek zonder contrastmiddel, indien de reductie van diagnostische kwaliteit acceptabel is.

Indien de vorige overgevoeligheidsreactie mild was:
- Voer het radiologisch onderzoek uit zoals gebruikelijk
- Observeer de patiënt ≥ 30 minuten met het infuus in.
- Wees waakzaam om te reageren op een mogelijke nieuwe overgevoeligheidsreactie.

Indien de vorige overgevoeligheidsreactie matig-ernstig was:
- Geef premedicatIe: 50 mg prednisolon IV** en 2mg clemastine IV binnen 30min voorafgaand aan CM toediening.
- Voer het radiologisch onderzoek uit zoals gebruikelijk
- Observeer de patiënt ≥ 30 minuten met het infuus in.
- Wees waakzaam om te reageren op een mogelijke nieuwe overgevoeligheidsreactie.

Indien de vorige overgevoeligheidsreactie ernstig was:
- Geef premedicatIe: 50 mg prednisolon IV** en 2mg clemastine IV binnen 30min voorafgaand aan CM toediening.
- Voer het radiologisch onderzoek uit zoals gebruikelijk
- Observeer de patiënt ≥ 30 minuten met het infuus in.
- Wees waakzaam om te reageren op een mogelijke nieuwe overgevoeligheidsreactie.

III Patiënten met eerdere doorbraakreacties op ICM of GBCA

Pas dezelfde aanbevelingen toe als hierboven bij patiënten met doorbraakreactie na ICM of GBCA toediening.

Verwijs patiënten met doorbraakreacties altijd door naar een specialist in geneesmiddelenovergevoeligheid voor huidtesten met verschillende ICM of GBCA.

IV Patiënten met eerdere overgevoeligheidsreacties op meerdere CM

Pas dezelfde aanbevelingen toe als hierboven bij patiënten met overgevoeligheidsreacties voor meerdere CM (twee ICM, twee GBCA of een GBCA en een ICM).

Verwijs patiënten met overgevoeligheidsreacties voor meerdere CM altijd door naar een specialist in geneesmiddelenovergevoeligheid voor huidtesten met verschillende ICM of GBCA.

V Patienten met eerdere niet-ernstige late overgevoeligheidsreacties op ICM of GBCA

Bij patienten met een eerdere milde of matig-ernstige late overgevoeligheidsreactie op jodiumhoudende CM of gadolinium-houdende CA wordt premedicatie niet aanbevolen, zelfs niet in spoed of acute onderzoeken.

Voetnoten

* Houdt rekening met kruis-reactiviteit van ICM (zie Introductie van deze sectie, tabel 2).

**Of equivalente dosis van een ander glucocorticosteroid
25 mg of 50 mg prednisolon is equivalent aan:

- 20 mg of 40 mg methylprednisolon.
- 4 mg of 8mg dexamethason.
- 100 mg of 200mg hydrocortison.

Aanbevelingen overgevoeligheidsreacties na niet-vasculaire CM toediening

Kleine hoeveelheden van ICM of GBCA kunnen worden geabsorbeerd door mucosa en dringen door tot de systemische circulatie na alle typen niet-vasculaire CM-toediening.

Overgevoeligheidsreacties na niet-vasculaire CM toediening van ICM of GBCA kunnen voorkomen, maar hun incidentie is laag tot zeer laag.

Geen preventieve maatregelen zijn geïndiceerd voor ERCP of voor niet-vasculaire GBCA toediening.

Voor andere indicaties van ICM kan geen duidelijke aanbeveling worden gegeven voor patiënten die in het verleden een overgevoeligheidsreactie na contrasttoediening hebben gehad.

Bij patiënten die een ernstige overgevoeligheidsreactie na contrasttoediening hebben gehad, dient de mogelijkheid van alternatieve beeldvorming of contrastmiddel te worden overwogen samen met een radioloog, en een strikte indicatie voor het gebruik van niet-vasculaire CM toediening is noodzakelijk.

Bij patiënten die een ernstige overgevoeligheidsreactie na contrasttoediening hebben gehad kunnen de preventieve maatregelen zoals beschreven in Module 5 worden gevolgd vooraf aan het onderzoek met niet-vasculaire CM-toediening. Indien mogelijk na laboratorium- en huidtesten door een specialist in geneesmiddelovergevoeligheid.

Samenvatting van aanbevelingen voor beeldvorming met GBCA

Module 6: Uitgangsvraag
Hoe kan post-contrast acute nierschade (PC-AKI) worden voorkomen bij toediening van Gadolinium-Based Contrast Agents (GBCA)?

Aanbevelingen

Gebruik de optimale GBCA dosis gebaseerd op gewicht van de patiënt die nodig is om een diagnostische MRI te verrichten in lokale doseringsprotocollen.

Pas geen profylactische maatregelen toe om PC-AKI te voorkomen bij hoog-risico patiënten (eGFR<30ml/min/1.73m^2) die GBCA IV krijgen in een standaard dosis.

Vervang geen ICM door GBCA om PC-AKI te voorkomen bij CT en/of DSA.

Module 7: Uitgangsvragen
a) Welke patiënten hebben en verhoogd risico op het ontwikkelen van Nephrogenic Systemic Fibrosis (NSF)?
b) Welke maatregelen zijn nodig om NSF te voorkomen?

Aanbevelingen

Gebruik laag-risico (ionisch en non-ionisch) **macrocyclische** GBCAs voor medische beeldvorming bij alle patiënten. Lineaire GBCA is geassocieerd met NSF, daarom dient **lineaire** GBCA enkel overwogen te worden indien een macrocyclisch GBCA de diagnostische vraag niet kan beantwoorden.

Maak een individuele risico-voordeel analyse met de aanvragend arts van de patiënt en met een nefroloog om verzekerd te zijn van een strikte indicatie voor MRI met **lineaire** GBCA bij patiënten met eGFR < 30 ml/min/1.73m^2.

Voor preventie van NSF bij patiënten die al afhankelijk zijn van hemodialyse of peritoneale dialyse, hoeft de toediening van **macrocyclische** GBCA niet direct gevolgd te worden door een hemodialyse sessie.

Om de hoeveelheid circulerend GBCA te minimaliseren, dient bij patiënten die al chronische hemodialyse ondergaan de toediening van **lineaire** GBCA direct te worden gevolgd door een (high-flux) hemodialyse sessie, wat herhaald wordt in de twee opeenvolgende dagen.

Bij predialyse patienten (eGFR<15 ml/min/1.73m^2) en peritoneaal dialyse patienten dient het risico op NSF door **lineaire** GBCA te worden afgewogen tegen het risico van het plaatsen van een tijdelijke centraal veneuze toegang voor hemodialyse.

Module 8: Uitgangsvraag
Wat is de klinische relevantie van de GBCA-geïnduceerde T1w hyperintensiteit van de nucleus dentatus en de globus pallidus in de hersenen?

Aanbevelingen

Zorg voor een strikte indicatie voor met gadolinium versterkte MRI en gebruik door de EMA goedgekeurde GBCA bij alle patiënten om mogelijke gadolinium depositie te minimaliseren.

Samenvatting van aanbevelingen voor andere onderwerpen

Module 9: Uitgangsvraag

Hoe kunnen centraal veneuze katheters (CVC), hemodialyse katheters (HC), perifeer ingebrachte centrale katheters (PICC), en totally implantable venous access devices (TIVAD, poorten) veilig worden gebruikt voor het toedienen van intraveneuze CM, in het bijzonder bij het gebruik van power injectors en hogere injectiesnelheden voor het verkrijgen van afbeeldingen van hoge kwaliteit?

Aanbevelingen

Opmerking: Hoge beeldkwaliteit is meestal nodig bij laag-contrast situaties, zoals bij (stagerings)onderzoeken in de hersenen, in het hoofd-hals gebied of bij hepatobiliaire, genito-urinaire of colorectale onderzoeken in het abdomen. Lagere beeldkwaliteit kan acceptabel zijn in hoog-contrast situaties zoals bij pulmonaire of musculoskeletale beeldvorming, of bij de follow-up van lymfeklieren (bv. lymfomen, testiscarcinoom).

Gebruik een power-injector en perifere veneuze katheter voor intraveneuze CM toediening om de beste kwaliteit van beedlvorming na contrasttoediening te verkrijgen, vooral in laag-contrast situaties (zie Opmerking).

Controleer voor én na CM toediening met een power injector de positie en doorgankelijkheid van een CVC, TIVAD of PICC lijn wanneer een perifere veneuze katheter niet beschikbaar is.

Power-injecteerbare centraal veneuze catheters kunnen veilig worden gebruikt voor de toediening van CM met een power-injector wanneer de meeste recente aanbevelingen van de fabrikant van de katheter worden opgevolgd.

Power-injecteerbare hemodialyse katheters kunnen veilig worden gebruikt voor de toediening van CM met een power-injector wanneer de meest recente aanbevelingen van de fabrikant van de katheter worden opgevolgd.

Wanneer CM wordt geïnjecteerd met een power-injector bij patiënten met een PICC lijn of TIVADs waarvan de kathertertip boven de tracheobronchiale hoek ligt is er risico op migratie van de kathetertip van deze lijnen. Controleer daarom bij een PICC of TIVAD met kathetertip boven de tracheobronchiale hoek de positie van de kathetertip met een röntgenfoto, CT instelopname, of doorlichting voor én na CM toediening met een power injector.

Wanneer een voor power-injectie geschikte CVC, HC, PICC of TIVAD wordt gebruikt voor CM toediening met een power-injector, controleer dan of de katheter nog open is door handmatig te spoelen met 20 ml fysiologisch zout na de injectie

Wanneer een voor power-injectie geschikte HC wordt gebruik voor CM toediening met een power injector, moet een patient-specifieke oplossing om de catheter af te sluiten direct na injectie worden aangelegd door een gecertifceerde dialyse verpleegkundige.

Zie Appendix 1 voor aanbevelingen over stroomsnelheden en injectiedruk voor een groot aantal commercieel beschikbare CVC's, HC's, PICC's en TIVAD's in Nederland.

Module 10: Uitgangsvraag
Wat is de optimale behandeling voor contrast media extravasatie?

Aanbevelingen

Overweeg de volgende behandelingsopties voor extravasatie met contrast:
- Probeer het extravasale contrastmiddel via een ingebrachte naald op te zuigen.
- Markeer het getroffen gebied.
- Gebruik kompressen voor het verlichten van pijn op de injectieplaats.
- Gebruik pijnstillers.
- Plaats de getroffen extremiteit boven het niveau van het hart.

Documenteer de contrast extravasatie en behandeling in het elektronisch patiënten dossier (volume, concentratie, oppervlakte, klinische bevindingen).

Geef de patiënt duidelijke instructies wanneer aanvullende medische zorg moet worden gezocht:
- Verergering van de symptomen.
- Huidulceratie.
- Ontwikkeling van eventuele neurologische of circulatoire symptomen, inclusief paresthesieën.
- Geef de patiënt schriftelijke informatie mee.

In geval van ernstige extravasatie schade:
- Consulteer een plastisch chirurg.
- Breng de verwijzend arts op de hoogte.

Overall Introduction

Reason for making this guideline
The Radiological Society of The Netherlands (RSTN - NVvR) deemed a set of new guidelines on the Safe Use of Contrast Media (CM) highly necessary and relevant, due to recent publications on many topics concerning contrast safety. Because of recent scientific developments, the recommendations of the most recent CM guideline (CBO, 2007) were in conflict with what should be considered best clinical practice. In order to update and elaborate on this 2007 CBO Guideline, which only covered selected topics on the use of iodine-containing CM, a plan has been developed to make a set of 3 new guidelines covering the safe use of all types of CM in adults.

The patient population for which these guidelines are meant consists of adult patients (18 years and older) who receive intravascular, oral or intracavitary (intra-articular, intra-vesical, intra-cholangiographic) contrast media both in the clinical setting, as well as for outpatients.
The guidelines do not cover radioactive contrast tracer use in nuclear medicine.

The three parts of the Safe Use of Contrast Media guidelines were planned to be produced and will cover following topics regarding CM safety (part 3 is still in the planning phase, topics to be finalized):

Safe Use of Contrast Media - Part 1 (finalized in 2017):
- Prevention of post-contrast acute kidney injury (PC-AKI) from iodine-containing contrast media.
- Iodine-containing contrast media use in patients with type-2 diabetes taking metformin.
- Iodine-containing contrast media use in patients on chronic dialysis.

Safe Use of Contrast Media - Part 2 (2016-2019):
- Prophylaxis and management of hypersensitivity reactions to contrast media.
- Safe use of gadolinium containing contrast media, in terms of prevention of post-contrast acute kidney injury (PC-AKI) and Nephrogenic systemic fibrosis (NSF).
- Contrast media injections with power injectors through (peripherally inserted) central venous lines and implantable ports.
- Contrast media extravasation.

Safe Use of Contrast Media - Part 3 (2020-2022):
- Prevention of iodine-induced hyperthyroidism.
- Safety of organ-specific gadolinium-based contrast agents.
- Gadolinium deposition in the body after gadolinium-based contrast agents.
- Contrast media use in pregnancy and during lactation.
- Contrast media use in patients with multiple myeloma (M. Kahler).
- Contrast media use in patients with pheochromocytoma.
- Contrast media use in patients with myasthenia gravis.
- Contrast media use in patients with mastocytosis.
- The Weber and Lalli effects in using contrast media.

The nephrotoxicity of gadolinium-based contrast media and/or microbubble contrast media and the recommendations for measurement of eGFR will be integrated with the guidelines for prevention of Nephrogenic Systemic Fibrosis. These recommendations are published in this guideline Safe Use of Contrast Media, part 2.

Goal of the current guideline
The aim of the Part 2 of Safe Use of Contrast Media guidelines is to critically review the present recent evidence with the above trend in mind and tries to formulate new practical guidelines for all hospital physicians to provide the safe use of contrast media in diagnostic and interventional studies. The ultimate goal of this guideline is to increase the quality of care, by providing efficient and expedient healthcare to the specific patient populations that may benefit from this healthcare and simultaneously guard patients from ineffective care. Furthermore, such a guideline should ideally be able to save money and reduce day-hospital waiting lists.

Focus of the guideline
This part 2 of the Safe Use of Contrast Media guideline focuses on all adult (18 years and older) patients that receive CM during radiologic or cardiologic studies or interventions.

Users of this guideline
This guideline is intended for all hospital physicians that request or perform diagnostic or interventional radiologic or cardiologic studies for their patients in which CM are involved.

Terminology and definitions
The terminology and definitions will be discussed in the introductory chapters of each of the 4 subtopics of this guideline.

Guideline Disclaimers
General
The aim of clinical guidelines is to help clinicians to make informed decisions for their patients. However, adherence to a guideline does not guarantee a successful outcome. Ultimately, healthcare professionals must make their own treatment decisions about care on a case-by-case basis, after consultation with their patients, using their clinical judgement, knowledge and expertise. A guideline cannot replace a physician's judgment in diagnosing and treatment of particular patients.

Guidelines may not be complete or accurate. The Working Group of this guideline and members of their boards, officers and employees disclaim all liability for the accuracy or completeness of a guideline, and disclaim all warranties, express or implied to their incorrect use.

Guidelines users always are urged to seek out newer information that might impact the diagnostic and treatment recommendations contained within a guideline.

Individualisation
In specific high-risk patient groups clinicians may have to regress from these general guidelines and decide on individualisation to best fit the needs of their patients.

Life-threatening situations or conditions
In acute life-threatening situations or conditions clinicians may have to regress from these general guidelines and decide on individualisation to best fit the needs of their patients in these situations or conditions.

Abbreviations Used in this Guideline

ACR	American College of Radiology
ADR	Adverse Drug Reaction
AGEP	Acute Generalized Exanthematous Pustulosis
AGREE	Appraisal of Guidelines for Research & Evaluation
BAT	Basophil Activation Test

CA	Contrast Agent
CI	Confidence Interval
CM	Contrast Medium/Media
CT	Computed Tomography
CVC	Central Venous Catheter
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
DSA	Digital Subtraction Angiography
DX	Digital Radiography
EAACI	European Association of Allergy and Clinical Immunology
EEM	Erythema Exsudativa Multiforme
EMA	European Medicines Agency
ENDA	European Network for Drug Allergies
ESUR	European Society of Urogenital Radiology
FDE	Fixed Drug Eruption
GBCA	Gadolinium-Based Contrast Agent/Agents
Gd	Gadolinium
GRADE	Grades of Recommendation, Assessment, Development, and Evaluation
HC	Haemodialysis Catheter
HSR	Hypersensitivity Reaction/Reactions
ICM	Iodine-based Contrast Medium/Media
IDT	Intradermal Test
IgE	Immunoglobulin E
IM	Intramuscular
IV	Intravenous
LAREB	Landelijke Registratie en Evaluatie Bijwerkingen
MRI	Magnetic Resonance Imaging
NPV	Negative Predictive Value
NSF	Nephrogenic Systemic Fibrosis
NVvR	Nederlandse Vereniging voor Radiologie
OBS	Observational Study
OR	Odds Ratio
PC-AKI	Post-Contrast Acute Kidney Injury
PICC	Peripherally Inserted Central Catheter
PO	Peroral
PPV	Positive Predictive Value
PSI	Pounds per Square Inch
RCT	Randomized Clinical Trial
RF	Fluoroscopy
RSTN	Radiological Society of The Netherlands
SD	Standard Deviation
SJS	Stevens-Johnson Syndrome
SPT	Skin Prick Test
SR	Systematic Review
TEN	Toxic Epidermal Necrolysis
TIVAD	Totally Implantable Venous Access Device
US	Ultrasound
WAO	World Allergy Organisation

Justification of the guideline

Validity
The board of the Radiological Society of the Netherlands will determine at the latest in 2024 if this guideline (per module) is still valid and applicable. If necessary, a new working group will be formed to revise the guideline. The validity of a guideline can be shorter than 5 years, if new scientific or healthcare structure developments arise, that could be seen as a reason to commence revisions. The Radiological Society of the Netherlands is considered the keeper of this guideline and thus primarily responsible for the actuality of the guideline. The other scientific societies that have participated in the guideline development share the responsibility to inform the primarily responsible scientific society about relevant developments in their field.

Initiative
Radiological Society of the Netherlands

Authorization
The guideline is submitted for authorization to:

- Radiological Society of the Netherlands
- Netherlands Association of Internal Medicine
- Dutch Federation of Nephrology
- Dutch Society of Intensive Care
- Association of Surgeons of the Netherlands
- Netherlands Society of Cardiology
- Netherlands Society of Intensive Care
- Dutch Association of Hospital Pharmacists
- Netherlands Society of Emergency Physicians
- Dutch Society for Allergology and Clinical Immunology
- Dutch Society for Dermatology and Venereology

General Information
The guideline development was assisted by the Knowledge Institute of the Federation Medical Specialists (www.kennisinstituut.nl) and was financed by the Quality Funds for Medical Specialists (Stichting Kwaliteitsgelden Medisch Specialisten: SKMS).

Working group members
A multidisciplinary working group was formed for the development of the guideline in 2016. The working group consisted of representatives from all relevant medical specialization fields that are involved with intravascular contrast administration.

All working group members have been officially delegated for participation in the working group by their scientific societies. The working group has developed a guideline in the period from May 2016 until July 2019.

The working group is responsible for the complete text of this guideline.

Conflicts of interest

The working group members have provided written statements about (financially supported) relations with commercial companies, organisations or institutions that are related to the subject matter of the guideline. Furthermore, inquiries have been made regarding personal financial interests, interests due to personal relationships, interests related to reputation management, interest related to externally financed research and interests related to knowledge valorisation. The statements on conflict of interest can be requested at the administrative office of the Knowledge Institute of Medical Specialists and are summarised below.

Last name	*Function*	*Other positions*	*Personal financial interests*	*Personal relations*	*Reputation management*	*Externally financed research*	*Knowledge valorisation*	*Other interests*	*Signed*
Van der Putten	Internist nephrologist	None	None	None	None	None	None	None	14-10-2015
Van der Vlugt	Cardiologist	None	None	None	Chairman of the working group Cardiac MRI & CT and Nuclear imaging of the Netherlands Society of Cardiology	None	None	None	03-01-206
Roodheuvel	Emergency physician	Instructor OSG/VvAA for courses on echography – paid position Member of department for burn treatment – unpaid.	None	None	None	None	None	None	21-12-2015
Geenen	Radiologist	Member of commission prevention of PC-AKI	None	None	None	None	None	Has held several presentation about contrast media on invitation (GE, BAYER)	25-3-2016
Zielhuis	Hospital pharmacist	None	In the past (2013-2015) has participated in an advisory panel on expensive medication for the companies AbbVie and Novartis. Has received an expense allowance for this.	None	None	None	None	None	8-1-2016

			Both forms do not produce contrast media that this guideline is about. Currently not active in an advisory panel.						
De Geus	Internist-Intensivist Erasmus MC Rotterdam	None	None	None	None	None	None	None	Ja, 31-03-2016
Dekkers	Radiologist in training and PhD-candidate	None	None	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Ja, 8-7-2016
Wikkeling	Vascular surgeon	None	None	None	None	None	None	Not applicable	19-7-2016
Dekker	Radiologist	None	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	10-7-2016
Van der Molen	Chairman Radiologist at LUMC	None	None	None	None	None	Not applicable	One-off royalties Springer Verlag (2014) Reference work Safety of contrast medicine One-off payment by Guerbet for (2014) reference card management of CM reactions (educative material) Incidental payments for presentations or being day chairman at contrast safety congress (2016 Netherlands + Europe all firms: GE, Guerbet, Bracco, Bayer	6-9-2016
Kardaun	Dermatologist -	Replacing dermatologist	None	None	None	None	None	None	24-2-

	researcherUniversitair Medisch Centrum Groningen: unpaid	in clinical practice - unpaid Member of scientific advisory board of Lareb (Dutch center for pharmacovigilance): unpaid							2016
Brummer	Emergency physician Treant zorggroep location Emmen and Stadskanaal	None	None	None	None	None	None	None	23-2-2018

Input of patient's perspective
It was challenging to find representation for the patient's perspective, since the guideline does not discuss a specific group of patients with a disease. The Dutch Kidney Patients Association was invited to participate in an advisory board to the working group, but declined since this subject was not specific enough for them to give adequate input; The Dutch Kidney Patients Association did provide written feedback for specific modules during the commentary phase. The Dutch Kidney Patients Association and the Patient Federation of the Netherlands was invited to participate in the invitational conference in which the framework of the guideline was discussed. Furthermore, the concept guideline has been submitted for feedback during the comment process to the Patient Federation of the Netherlands and the Dutch Kidney Patient Association.

Implementation
In the different phases of guideline development, the implementation of the guideline, and the practical enforceability of the guideline were taken into account. The factors that could facilitate or hinder the introduction of the guideline in clinical practice have been explicitly considered. The implementation plan can be found with the Related Products. Furthermore, quality indicators were developed to enhance the implementation of the guideline. The indicators can also be found with the Related Products.

Methodology
AGREE
This guideline has been developed conforming to the requirements of the report of Guidelines for Medical Specialists 2.0 by the advisory committee of the Quality Counsel (www.kwaliteitskoepel.nl). This report is based on the AGREE II instrument (Appraisal of Guidelines for Research & Evaluation II) (www.agreetrust.org), a broadly accepted instrument in the international community and on the national quality standards for guidelines: "Guidelines for guidelines" (www.zorginstituutnederland.nl).

Identification of subject matter
During the initial phase of the guideline development, the chairman, working group and the advisor inventory the relevant subject matter for the guideline. Furthermore, an Invitational Conference was organized, where additional relevant subjects were discussed. A report of this meeting can be found in Related Products.

Clinical questions and outcomes
During the initial phase of guideline development, the chairman, working group and advisor identified relevant subject matter for the guideline. Furthermore, input was acquired for the outline of the guideline during an Invitational Conference. The working group then formulated definitive clinical questions and defined relevant outcome measures (both beneficial land harmful effects). The working group rated the outcome measures as critical, important and not important. Furthermore, where applicable, the working group defined relevant clinical differences.

Strategy for search and selection of literature
For the separate clinical questions, specific search terms were formulated and published scientific articles were sought after in (several) electronic databases. Furthermore, studies were scrutinized by cross-referencing for other included studies. The studies with potentially the highest quality of research were looked for first. The working group members selected literature in pairs (independently of each other) based on title and abstract. A second selection was performed based on full text. The databases, search terms and selection criteria are described in the modules containing the clinical questions.

Quality assessment of individual studies
Individual studies were systematically assessed, based on methodological quality criteria that were determined prior to the search, so that risk of bias could be estimated. This is described in the "risk of bias" tables.

Summary of literature
The relevant research findings of all selected articles are shown in evidence tables. The most important findings in literature are described in literature summaries. When there were enough similarities between studies, the study data were pooled.

Grading quality of evidence and strength of recommendations
The strength of the conclusions of the scientific publications was determined using the GRADE-method. GRADE stands for Grading Recommendations Assessment, Development and Evaluation (see http://www.gradeworkinggroup.org/) (Atkins, 2004).

GRADE defines four gradations for the quality of scientific evidence: high, moderate, low or very low. These gradations provide information about the amount of certainty about the literature conclusions. (http://www.guidelinedevelopment.org/handbook/).

Formulating conclusions
For diagnostic, etiological, prognostic or adverse effect questions, the evidence was summarized in one or more conclusions, and the level of the most relevant evidence was reported. For intervention questions, the conclusion was drawn based on the body of evidence (not one or several articles). The working groups weighed the beneficial and harmful effects of the intervention.

Considerations
Aspects such as expertise of working group members, patient preferences, costs, availability of facilities and organisation of healthcare aspects are important to consider when formulating a recommendation. These aspects were discussed in the paragraph Considerations.

Formulating recommendations
The recommendation answers the clinical question and was based on the available scientific evidence and the most relevant considerations.

Constraints (Organisation of healthcare)
During the development of the outline of the guideline and the rest of the guideline development process, the Organisation of healthcare was explicitly taken into account. Constraints that were relevant for certain clinical questions were discussed in the Consideration paragraphs of those clinical questions. The comprehensive and additional aspects of the Organisation of healthcare were discussed in a separate chapter.

Development of quality indicators
Internal (meant for use by scientific society or its members) quality indicators are developed simultaneously with the guideline. Furthermore, existing indicators on this subject were critically appraised; and the working group produces an advice about such indicators. Additional information on the development of quality indicators is available by contacting the Knowledge Institute for the Federation Medical Specialists. (secretariaat@kennisinstituut.nl).

Knowledge Gaps
During the development of the guideline, a systematic literature search was performed the results of which help to answer the clinical questions. For each clinical question the working group determined

if additional scientific research on this subject was desirable. An overview of recommendations for further research is available in the appendix Knowledge Gaps.

Comment- and authorisation phase

The concept guideline was subjected to commentaries by the involved scientific societies. The commentaries were collected and discussed with the working group. The feedback was used to improve the guideline; afterwards the working group made the guideline definitive. The final version of the guideline was offered for authorization to the involved scientific societies and was authorized.

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Introduction to hypersensitivity reactions to contrast media.

The increased use of contrast media (CM) may give rise to an increased occurrence of both mild and severe hypersensitivity reactions.

Terminology and Definitions
The following definitions and terminology are based on the standard terminology recommended by the World Allergy Organisation (Johansson, 2003; Johansson, 2004; Simons, 2011).

Hypersensitivity: Objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus that is tolerated by normal subjects.

Allergy: Hypersensitivity reactions initiated by specific immunological mechanisms.

Acute hypersensitivity reaction: an adverse reaction that occurs within 1 hour of contrast agent injection. Acute reactions can either be allergy-like (IgE-mediated or not) hypersensitivity reactions or chemotoxic responses.

Late hypersensitivity reaction: an adverse reaction that occurs between 1 hour and 1 week after contrast agent injection.

Anaphylaxis: A severe life threatening generalized systemic hypersensitivity reaction that is characterized by being rapid in onset with life-threatening airway breathing or circulatory problems and usually associated with skin and mucosal changes.

Adverse drug reaction (ADR): a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man (WHO definition).

The WAO has defined anaphylaxis as a serious allergic reaction that is rapid in onset and that can be fatal. For diagnosis, there are three possible clinical scenarios:
1. Sudden onset of an illness (minutes to hours) with involvement of the skin, mucosal tissue (or both), and at least one of the following: a) respiratory compromise and b) reduced blood pressure or symptoms of end-organ dysfunction.
2. Two or more of the following that occur after exposure to a likely allergen or other triggers (minutes to several hours): skin/mucosal symptoms and signs, respiratory compromise, reduced blood pressure or associated symptoms, and/or gastrointestinal symptoms (crampy abdominal pain or vomiting).
3. Reduced blood pressure after exposure to a known allergen (minutes to hours).

<u>Acute hypersensitivity reactions to contrast media</u>
Pathophysiology
Hypersensitivity reactions to CM are poorly understood. Recent research suggests that hypersensitivity reactions to nonionic CM are a heterogeneous disease. It can develop from multiple mechanisms such as IgE-dependent, complement dependent, direct membrane effects of CM, and possibly other mechanisms that have not been identified yet (Zhai, 2017). When an immunologic mechanism is excluded, unlikely or cannot be proven, hypersensitivity is the preferred term (Johansson, 2003; Johansson, 2004).

Allergy-like hypersensitivity reactions may or may not be true IgE-mediated. In general, allergy can be either antibody- or cell-mediated. Cell-mediated reactions occur usually after one or several days, while antibody mediated reactions tend to be more immediate. A well-known reason for immediate reactions is the presence of antigen-specific IgE antibodies fixed to the surface of mast cells and

basophil granulocytes. After cross-linking of IgE antibodies on the surface of these cells a degranulation process follows, resulting in production of histamine and many other mediator substances. Other stimuli can also cause degranulation such as degree of ionization, osmolality, temperature of the injected solution. Some drugs such as opiates are known to cause histamine production without the presence of specific IgE.

Compared to reactions to iodine-based CM, reactions to gadolinium-based CA are more frequently IgE-mediated, and thus true allergic reactions.

Note: Not all symptoms experienced by patients in the hour after contrast agent injections are adverse reactions to the contrast agent. Patient anxiety may cause symptoms after contrast agent administration, known as the Lalli effect (Lalli, 1974).

Clinical features and risk factors
The same acute adverse reactions are seen after intravascular administration of iodine-based contrast media and after gadolinium-based contrast agents or ultrasound contrast agents.

The term *adverse drug reaction (ADR)* is wider than hypersensitivity reactions, and includes a number of chemotoxic effects of CM injection, such as a feeling of warmth, dry mouth, or mild pain during injection, etc. Therefore, incidence figures between studies on hypersensitivity reactions and studies on ADR (for example post-marketing surveillance studies) can vary.

Mild reactions include allergy-like reactions such as limited urticaria/pruritus, limited cutaneous oedema, itchy/scratchy throat, nasal congestion, and sneezing/conjunctivitis/rhinorrhoea. In this category are included also physiologic/chemotoxic reactions such as limited nausea/vomitus, transient flushing/warmth/chills, headache/dizziness/anxiety, altered taste, mild hypertension or spontaneously resolving vasovagal reactions (ACR Manual on contrast media; ESUR guidelines on contrast safety; Wang 2008).

Moderate reactions include allergy-like reactions such as diffuse urticaria/pruritus, diffuse erythema with stable vital signs, facial oedema without dyspnoea, throat tightness/hoarseness without dyspnoea, mild wheezing/bronchospasm. Physiologic reactions are protracted nausea/vomitus, hypertensive urgency, isolated chest pain, and vasovagal reactions responsive to treatment (ACR Manual on contrast media; ESUR guidelines on contrast safety; Wang 2008).

Severe reactions include allergy-like reactions such as diffuse erythema with hypotension, diffuse/facial oedema with dyspnoea, laryngeal oedema with stridor, and severe wheezing/bronchospasm with hypoxia, and generalized anaphylactic reaction/shock. Physiologic reactions are treatment-resistant vasovagal reactions, arrhythmia, hypertensive emergencies, and convulsions/seizures. Also to this category belong pulmonary oedema and cardiopulmonary arrest (ACR Manual on contrast media; ESUR guidelines on contrast safety; Wang 2008).

<u>Risk factors</u>
Risk factor analysis is often done by retrospective observational studies without control groups.

The most common risk factors for hypersensitivity reactions to CM are (ACR Manual on contrast media; Lalli, 1980):
1. A prior hypersensitivity reaction to contrast media.
2. A history of allergy, particularly multiple severe allergies.
3. A history of asthma requiring treatment.

Female gender could not be substantiated as an independent risk factor for hypersensitivity reactions.

Incidence of acute hypersensitivity reactions

Incidence after iodine-based contrast media

The incidence is highest after iodine-based contrast media and lowest after ultrasound contrast agents. The incidence of acute adverse reactions has declined considerably after the introduction of low-osmolar and iso-osmolar iodine-based contrast media (ACR Manual on contrast media; ESUR guidelines on contrast safety).

In the early days of low-osmolar media, the classic Japanese study by Katayama (1990) reported relatively high adverse drug reactions after nonionic CM in up to 3,1%, with severe and very severe reactions occurring in 0,44%. In contrast, more recent studies with large patient cohorts focusing more specifically on hypersensitivity (allergic-like) reactions have shown considerably lower incidence rates of 0,15 to 0,69% with severe reactions occurring in 0,005 to 0,013% (Hunt, 2009; Mortele, 2005; Wang, 2008).

Hypersensitivity reactions after non-vascular CM administration (either oral, rectal, intraductal, intravesical or intra-articular) are rare. Such reactions occur slower and the incidence is much lower than after intravascular administration and will be influenced by the integrity and condition of the wall of the cavity into which the contrast agent is administered (for example inflamed mucosa may lead to leakage into the intravascular compartment). Nevertheless, severe reactions can occur, even with non-vascular CM administration (Davis, 2015).

Incidence using specific iodinated contrast media

Large post-marketing surveillance studies of iobitridol and iodixanol have shown acute adverse events of 0,58-0,59% with severe events in 0,004 to 0,010% (Maurer, 2011; Zhang, 2014). A third study using iopromide is more difficult to compare due to different definitions, and had higher rates of 2,49% and 0,034%, respectively (Palkowitch, 2014). It must be noted that chemotoxic reactions (feeling of warmth, metallic taste) make up a considerable part of these events.

In addition, a number of retrospective, observational studies have looked at differences in acute hypersensitivity rates among iodine-based CM. Although imperfect, these studies indicate a somewhat higher rate for iopromide and iomeprol compared to other CM (Gomi, 2010; Kim; 2017; Seong, 2014). It remains controversial whether iobitridol has a lower percentage, as indicated in one study (Kim, 2017).

Incidence after gadolinium-based contrast agents

Recent studies with large adult patient cohorts focusing on hypersensitivity (allergic-like) reactions have shown low incidence rates of 0,06-0,17% with severe reactions occurring in 0,003 to 0,006% (Aran 2015; Behzadi, 2018; Dillman, 2007; Prince, 2011). In a recent large meta-analysis, the overall rate was 92 per 100,000 gadolinium-based contrast agent (GBCA) injections (0,09%) with severe reactions occurring in 5,2 per 100,000 injections (0,005%) (Behzadi, 2018).

In that meta-analysis it was shown that the type of GBCA is of influence on the number of reactions. Linear nonionic GBCA had an incidence of 15 per 100,000 and linear ionic GBCA of 52 per 100,000. However, these GBCA are no longer available in Europe. The macrocyclic GBCA had slightly higher rates, macrocyclic ionic 90 per 100,000 and macrocyclic nonionic 160 per 100,000.

The highest rate was for linear ionic with protein-binding, 170 per 100,000 injections (Behzadi, 2018).

A new, large, retrospective study analysed 281,945 GBCA injections. The overall rate of hypersensitivity reactions was 156 per 100,000 GBCA injections. Severe reactions occurred in only 2,1 per 100,000 injections. Relatively more hypersensitivity reactions occurred after gadobenate and gadobutrol compared with gadodiamide or gadoterate injection (McDonald, 2019).

Breakthrough, Protracted and Biphasic Hypersensitivity Reactions

So-called "breakthrough" hypersensitivity reactions are recurring reactions despite premedication with corticosteroids and H1-antihistamines. The occurrence in published series is 2 to 17%. These reactions are most often of similar severity as the original (culprit) reaction for which premedication was prescribed. Breakthrough reactions can be severe in incidental cases (Davenport, 2009; Mervak, 2015).

While the majority of hypersensitivity reactions to CM are uniphasic, other patterns may also occur. A *protracted* reaction is defined as a reaction lasting > 5h in which symptoms incompletely resolve. This pattern is rare following CM, occurring in only 4% of anaphylactic (severe) reactions and may be predicted by a low responsiveness to initial adrenaline therapy (Kim, 2018).

A *biphasic* reaction is defined as a reaction recurring 0 to 72h after an initial hypersensitivity reaction. The median time for start of the second reaction is 8 to 12h after the first reaction. This pattern is also rare, occurring in 10% of anaphylactic (severe) reactions. Usually, the second reaction is of similar severity or milder than the initial reaction. Predictors for biphasic anaphylaxis are severe initial symptoms requiring adrenaline redosing or a long (> 40 min) duration of the initial reaction. An observation time of 6-12h after the initial anaphylactic reaction has resolved is practical (Lee, 2016; Kim, 2018; Kim, 2019). Corticosteroids may have some benefit in the prevention of a biphasic anaphylactic reaction with relatively few side effects, but this remains controversial (Simons, 2015; Lee, 2016).

For ultrasound contrast agents the risk is low, but no large series have been published to date. Most adverse reactions are cardiovascular, and the incidence of hypersensitivity reactions is 0,009% with severe reactions occurring in 0,004% (Khawaja, 2010).

Classification

Historically, hypersensitivity reactions to CM have been graded as mild, moderate or severe. This radiological classification shows overlap with other used classifications, such as the World Allergy Organisation (WAO) classification (Johansson, 2003; Johansson, 2004) and modifications of the Ring - Messmer classification of allergic reactions (Ring, 1977).

Table 1 ***Severity grading of anaphylactic reactions*** **(modified Ring and Messmer):**

Grade	Skin	Abdomen	Airways	Cardiovascular
I	Itch Flush Urticaria Angioedema	-	-	-
II	Itch Flush Urticaria Angioedema	Nausea Cramps	Rhinorrhoea Hoarseness Dyspnoea	Tachycardia (> 20 bpm) Hypertension (>20 mm Hg) Arrhythmia
III	Itch Flush Urticaria Angioedema	Vomitus Defecation	Laryngeal oedema Bronchospasm Cyanosis	Shock
IV	Itch Flush Urticaria Angioedema	Vomitus Defecation	Respiratory arrest	Cardiac arrest

Classification according to the most severe symptom, no symptom is mandatory

A practical classification of acute hypersensitivity reactions to contrast media for radiological practices may be (free after ACR Manual on contrast media; ESUR guidelines on contrast safety):

Mild: Itching, sneezing, flushing, conjunctivitis, rhinorrhoea, epiphora, nausea, short-duration or incidental vomiting, altered taste, limited scattered urticaria (10 or less).

Moderate: Generalized or extensive urticaria, diffuse erythema without hypotension, facial or angioedema without dyspnoea, mild wheezing/bronchospasm, protracted vomiting, mild isolated hypotension.

Severe: Severe wheezing/bronchospasm, profound hypotension, pulmonary oedema, generalized anaphylactic reaction, seizures/convulsions, respiratory arrest, and cardiac arrest.

Late Hypersensitivity Reactions to Contrast Media

Pathophysiology

There is evidence that drug-specific T-cells play an important role in late hypersensitivity reactions. In skin reactions an infiltrate in the dermis consisting of activated CD4+ or CD8+ T-cells and eosinophilic leucocytes is usually found (Christiansen, 2000; Christiansen, 2003).

In vitro studies have shown two different pathways of CM recognition which both require major histocompatibility complex (MHC) molecules for stimulation: a) direct binding of CM to the T-cell receptor (p-i concept), and b) after uptake and processing by antigen-presenting cells and presented to T-cells via MHC-II molecules ((pro)hapten concept (Keller, 2009)).

The hapten-independent pathway could explain results of cross-reactivity analyses that revealed that CM-specific activated T-cell clones reacted to CM with shared structural elements.

It has been postulated that CM do not induce a primary immune response, but instead interact with receptors on activated memory T-cells raised against other foreign substances. For this reason, patients with late hypersensitivity should not be at risk for an immediate or late anaphylactic reaction (mediated by IgE or other mechanisms) upon re-exposure to CM.

Clinical features and risk factors

Many patients show a variety of nonspecific symptoms, which include headache, nausea, dizziness, gastro-intestinal upset, mild fever, and arm pain (Bellin, 2011; Christiansen, 2000). When compared to control populations (Loh, 2010), skin rashes with erythema and swelling are the most frequent true late hypersensitivity reactions. Most patients present with cutaneous symptoms similar to other drug-induced skin eruptions, usually in the form of a macular or maculopapular exanthema. The exanthema usually occurs 2 to 10 days after first exposure to ICM and 1 to 2 days after re-exposure to the same ICM. Most reactions are mild to moderate in severity, are usually self-limiting and resolve within 1 week (Bellin, 2011).

Other skin reactions include fixed drug eruptions (FDE), erythema exudativa multiforme (EEM) and scaling skin eruptions. In rare cases severe reactions have been described, such as drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, toxic epidermal necrolysis (TEN), acute generalized exanthemic pustulosis (AGEP), and Stevens-Johnson syndrome (SJS).

Established risk factors for late hypersensitivity reactions to iodine-based CM include a previous hypersensitivity reaction and IL-2 immunotherapy (ACR Manual on contrast media; Bellin (2011); ESUR guidelines on contrast safety).

Patients with a history of late hypersensitivity reactions to ICM are not at increased risk for acute reactions to ICM as these reactions are mechanistically unrelated (Christiansen, 2003; Mazori, 2018).

Incidence of late hypersensitivity reactions

The frequency of late hypersensitivity reactions to CM varies greatly between studies and is believed to be between 1 to 3% of patients after iodine-based CM administration and only very rarely after gadolinium-based CA administration (Bellin, 2011; Christiansen, 2000).

Incidence using specific iodine-based CM

Late skin reactions tend to be more common after iodixanol (Benin, 2011; Sutton, 2003). The incidence of late hypersensitivity reactions is not significantly different for the other iodine-based low-osmolar CM (Bellin, 2011).

Cross-reactivity between contrast media

Cross-reactivity between iodine-based CM

Most of the current cross-reactivity data come from skin testing. Cross-reactivity in late hypersensitivity reactions is probably caused by the presence of CM-specific T-cells, some of which may show a broad cross-reactivity pattern. There may be a link between the chemical structure of iodine-based CM and the pattern of cross-reactivity, but results are not consistent.

Several studies have shown considerable cross-reactivity between different iodine-based CM, but specific data on acute versus late hypersensitivity reactions are lacking until now. In the larger studies, most cross-reactivity has been seen between the nonionic dimer iodixanol and its monomer iohexol, with relatively fewer positive skin reactions with iobitridol (Hasdenteufel, 2011; Lerondeau, 2016).

Based on cross-reactivity patterns Lerondeau, et al divided iodine-based CM in three groups, with relatively high intra-group cross-reactivity but less intergroup cross-reactivity (Lerondeau, 2016). Based on additional data, it seems reasonable to add iopromide to group A as well (Schrijvers, 2018). Table 2 may be helpful for selecting an alternative agent for imaging studies.

Table 2 Cross-reactivity grouping of iodine-based CM

Group A	Group B	Group C
Ioxithalamate (Telebrix)	Iobitridol (Xenetix)	Amidotrizoate (Gastrografin)
Iopamidol (Iopamiro)	Ioxaglate (Hexabrix)	
Iodixanol (Visipaque)		
Iohexol (Omnipaque)		
Ioversol (Optiray)		
Iomeprol (Iomeron)		
Iopromide (Ultravist)		

Cross-reactivity between gadolinium-based CM

Information on cross-reactivity between GBCA is limited to case reports. Skin testing and provocation tests in such cases have shown that cross-reactivity among macrocyclic GBCA does exist.

Cross-reactivity between iodine-based and gadolinium-based CM

A recent study examined the risk of reactions to both iodine-based CM and gadolinium-based CA in the same patient in a large patient cohort. The incidence of primary hypersensitivity reactions was 0,047% and the incidence of secondary reactions 0,024%. Nearly all reactions were mild, requiring no treatment. Therefore, cross-reactivity between iodine-based and gadolinium-based CM is an extremely rare event (Sodagari, 2018).

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Module 1 Management of acute hypersensitivity reactions

Research question

What is the optimal treatment for acute hypersensitivity reactions to contrast media?

Introduction

Acute hypersensitivity reactions often create stress and confusion and appropriate training and clear protocols are advisable. In addition, depending on the location where a patient suffers an acute hypersensitivity reaction to contrast media, the available expertise of the personnel that cares for such a patient may differ. Similarly, the availability of equipment and drugs to treat a (possible serious) hypersensitivity (or anaphylactic) reaction will be different. In a radiology or cardiology department the possibilities are different (and usually more limited) than in a department of emergency medicine or on a hospital ward. In addition, different treatments will have variable modes of action. What is the most appropriate management of a patient with an acute hypersensitivity reaction to contrast media?

Search and select criteria

To answer the clinical question a systematic literature analysis was performed.

P (Patient):	patients with acute hypersensitivity reaction after contrast media administration;
I (Intervention):	treatment, antihistamines, corticosteroids, epinephrine, adrenalin, dopamine, norepinephrine, noradrenalin, histamine H1 antagonists, histamine H2 antagonists, H1 antihistamines, H2 antihistamines, adrenergic beta-2 receptor agonists, glucocorticoids, management/treatment of hypersensitivity reactions/allergic reactions after contrast media, antihistamines, volume resuscitation, bronchodilators;
C (Comparison):	conservative treatment or comparison of interventions mentioned above;
O (Outcomes):	duration of acute reaction, severity of complaints, morbidity, mortality, costs, hospitalization in an IC-unit, length of stay.

<u>Relevant outcome measures</u>

The working group considered morbidity, mortality, and hospitalization in an IC-unit, critical outcome measures for the decision-making process, and duration of acute reaction, length of stay and costs important outcomes for the decision-making process.

<u>Methods</u>

The databases Medline (OVID) and Embase were searched from 1^{s} of January 1985 to 28th of December 2017 using relevant search terms for systematic reviews (SRs), randomized controlled trials (RCTs) and observational studies (OBS).

Search terms are shown under the Tab “Literature Search”. The literature search procured 328 hits: 20 SR, 64 RCTs and 224 OBS. Based on title and abstract a total of 47 studies were selected. After examination of full text all studies were excluded, and no studies definitely included in the literature summary.

4 studies describing treatment effects of acute adverse reactions were found. Although these studies did not fulfil the search criteria, a short description is included in the literature summary, due to lack of other evidence. Since no control groups were available, no evidence tables or risk of bias tables or conclusions of these studies are included.

Summary literature of studies with a control group
Not applicable. There were no studies investigating the research question. The non-comparative studies are briefly described in the table below.

Conclusions of studies with a control group
Not applicable. There were no studies investigating the research question.

The non-comparative studies are briefly described in the table below.

Table 1.1 Treatment effects of acute adverse reaction

Abbreviations: CM contrast media; CPR Cardio-Pulmonary Resuscitation; IV intravenous;

Reference	Total n (n men)	CM type	Acute reaction(s)	Treatment	Outcome	Remarks
Collins, 2009	9 (3)	LOCM or Gadolinium	Ranged from laryngeal oedema, hypotension, tachycardia, dyspnoea to hypoxia	All patients received epinephrine; seven 0.1 mg (recommended initial dose) and two 0.3mg. Oxygen, diphenhydramine, steroids	7/9 discharged in good condition on same day of CM administration 1/9 Intubation during transport to emergency department, admitted to ICU, discharged 5 days later in good condition 1/9 Full cardiac arrest; autopsy showed retroperitoneal haemorrhage as cause of death	4/9 patients had some form of cardiovascular side effects attributed to epinephrine (such as “chest tightness”)
Wang, 2008	11 (3)	Non-ionic iodinated contrast media	Ranged from erythema, hypotension, tachycardia, unresponsiveness, arrhythmia, cardiopulmonary arrest, nausea, diaphoresis, rash, hypotension, semi-responsiveness, dizziness, gagging and difficulty speaking, bronchospasm, chest pain, generalized seizure to facial oedema	Ranged from CPR, 1 mg of epinephrine IV, 1 mg of atropine IV, 50 mEq of sodium bicarbonate, 1 g 10% calcium chloride, 10 L of O2 by face mask, normal saline, 50% dextrose, 50 mg of diphenhydramine IV, 100 mg of diphenhydramine to 120 mg of methylprednisolone	2/10 returned to their normal baseline conditions within 1 hour. 6/10 manifestations resolved completely within 24 hours, despite their severe symptoms and often extensive treatment. 2/10 sequelae lasting more than 24 hours 1 unknown outcome	Allergic-type reactions occurred in 545/84,928 (0.6%) of IV injections of nonionic iodinated contrast media in adults. 221 received treatment.
Power, 2016	85 (sex unknown)	Gadobutrol	81 mild allergic-like reactions: urticaria, rash, pruritus, limited erythema, Localized facial oedema, itchy eyes, scratchy throat, sneezing, coughing 3 moderate reactions: erythema over the anterior chest with dyspnoea, rash and soft palate swelling, pruritic rash and throat tightness	Half of the patient with mild reaction received treatment with oral diphenhydramine All patients with moderate reactions received treatment with diphenhydramine. 50-minute resuscitation effort	All patients were discharged	

			1 severe: breathing and swallowing			
Piscaglia, 2006	29 (sex unknown)	SonoVue	Ranged from dyspnoea, bronchospasm, slight hypotension and bradycardia, clouding of consciousness, lumbar pain, severe hypotension, cutaneous rash to paraesthesia at the upper limbs	IV corticosteroids, antihistamines, 1 g of hydrocortisone, lying down with both legs raised, lying down.	All patients recovered	

Considerations

As there are no comparative studies investigating the research question, the recommendations in this national guideline are based mainly on results of observational studies and reviews (for example Cohan, 1996; Bang, 2013; Morzycki, 2017; Boyd, 2017) and of the recommendations of the American College of Radiology 2018 (Manual on Contrast Media v10.3) (ACR, 2018), the European Society of Urogenital Radiology 2018 (electronic v10) (ESUR, 2018), the International Consensus On Drug Allergy 2014 (Demoly, 2014), the World Allergy Organisation (WAO) Anaphylaxis Guidelines 2011, update 2015 (Simons, 2015), the European Association for Allergy and Clinical Immunology (EAACI) Guidelines 2014 (Moraro, 2014), and adapted to the Dutch situation (Het Acute Boekje, NIV 2017).

Because of the diminished frequency of acute adverse reactions to contrast media, there are now fewer opportunities for physicians to recognize and appropriately treat such adverse reactions. Reactions vary from very mild itching to anaphylactic shock. These reactions are often unpredictable; they can happen to people who have not been exposed to contrast media in the past. A mild reaction may be self-limited but can also develop quickly into a severe reaction. When a hypersensitivity reaction to a contrast medium occurs, there may be insufficient time or opportunity to study the treatment protocols and medication doses. It is therefore important for personnel to be prepared for any adverse reaction, to have clear treatment guidelines, and to have access to a rapid response team in case of an emergency. (Segal, 2011).

Because of this diminished frequency and lack of experience in treatment, major guidelines recommend to restricting adrenaline injection in the hands of non-experienced users to intramuscular administration route only.

Risk factors

Patients with a history of previous moderate or severe acute hypersensitivity reaction to an iodine-based contrast medium or gadolinium-based or ultrasound contrast agent, asthma requiring medical treatment and atopy requiring medical treatment are at increased risk (ESUR 2018; ACR 2018).

Prevention

Use a low-osmolar or iso-osmolar non-ionic iodine-based contrast medium. In patients at risk consider an alternative test not requiring a contrast agent of similar class.

For previous contrast agent reactors: use a different contrast medium/agent, preferably after consultation with a specialist in drug allergy

The radiology department should be prepared for an acute reaction. This requires regular and optimized training of personnel. See Chapter: Organisation of healthcare.

Note:

Instead of adrenaline 1:1,000 ampules for IM administration each department may also opt for selecting the (more expensive) adrenaline 1:1,000 auto-injectors, for example EpiPen (Asch 2017).

Recommendations

Preparation:

- Have the drugs (as a minimum requirement: adrenaline, salbutamol, H1-antihistamine (clemastine) IV, and corticosteroid IV (for example prednisolone), equipment and

protocol for treatment of an acute adverse reaction readily available in every room where contrast agents are administered.
- Adhere to local protocols for accessibility of a resuscitation and emergency response team.
- Keep every patient with an acute hypersensitivity reaction to CM in a medical environment for at least 30 minutes after contrast agent injection. Moderate and severe reactions need a prolonged observation.

Acute management general principles:
- Check and stabilize patient according to the ABCDE method.
- Stop infusing contrast agent and replace IV line with crystalloid.
- Dyspnoea or stridor: let patient sit up.
- Hypotension: keep patient in prone position, raise legs.
- Consider measuring serum tryptase (see recommendations in chapter Laboratory Diagnosis of Hypersensitivity Reactions to Contrast Media).
- Record acute allergic reactions in allergy registry (see chapter Organisation of Healthcare).

Note: After administration of clemastine the patient may no longer be able (or insured) to drive a car/motorcycle or to operate machinery.

Severe reactions:

<u>Cardiac or respiratory arrest:</u>
- Start CPR.
- Call the CPR team.

<u>Anaphylactic reaction or stridor:</u>
- Call rapid response team (SIT-team).
- Give oxygen 10 to 15L/min with non-rebreathing mask.
- Give 0.5mg adrenaline IM in lateral upper thigh.
- Give fluid bolus of crystalloid 500ml IV in 10 minutes, repeat as necessary.
- Consider nebulizing salbutamol 5mg or budesonide 2mg for stridor.
- Give clemastine 2mg IV.
- Consider to add corticosteroid, for example prednisolone 50mg IV.

*Or equivalent dose of other corticosteroid.

50 mg prednisolone is equivalent to:
- 40 mg methylprednisolone.
- 8mg dexamethasone.
- 200mg hydrocortisone.

- *Consider adding corticosteroids to prevent a biphasic or protracted anaphylactic reaction if initial symptoms are severe

Moderate reactions:

Consider transferring the patient to a department with facilities for monitoring of vital functions.

Isolated bronchospasm:
- Salbutamol 2.5 to 5mg nebulization in oxygen by facemask 10 to 15 L/min (nebulization is easier to administer and more effective than dose aerosol).
- In mild cases asthma patients may use their own salbutamol dose aerosol.
- In case of deterioration give adrenaline 0.5mg IM and consider calling rapid response

team.

Isolated facial oedema without stridor:

- Give oxygen 10 to 15L/min with non-rebreathing mask.
- Give clemastine 2mg IV.
- If oedema is severe or near airways or if stridor develops: treat as anaphylaxis.

Isolated urticaria/diffuse erythema:

- Give clemastine 2mg IV.
- If accompanied by hypotension: treat as anaphylaxis.

Isolated hypotension:

- Give bolus of crystalloid 500ml IV, repeat as necessary.
- If accompanied by bradycardia, consider atropine 0.5mg IV.
- If accompanied by other symptoms: treat as anaphylaxis.

Mild reactions

General:

- Mild reactions may only need reassurance.
- Observe vital signs until symptoms resolve.
- Do not remove IV access during observation.

Consider:

- Prescribing a non-sedating antihistamine, for example desloratadine 5mg PO (once daily) for mild allergic reactions.
- Ondansetron 4mg IV for protracted vomiting.

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Guideline Module Validity And Maintenance

Module[1]	Responsible authors)[2]	Authorisation Year	Next evaluation of validity of guideline	Frequency of evaluation of validity[3]	Who surveys the actuality of this guideline[4]	Relevant factors for changing recommendations[5]
Treatment of acute reactions	NVvR	2019	2024	5 years	NVvR	New scientific developments

[1] Name of module
[2] Responsible authors (per module)
[3] Time frame: Once every 6 months, year, two years, five years, longer
[4] Responsible scientific society
[5] Variety of reasons: new drugs, new therapies, et cetera

Module 2 Treatment of late reactions to contrast media

Research question

What is the optimal treatment for late hypersensitivity reactions to contrast media?

Introduction

Late (non-immediate) adverse reactions are heterogeneous. Because of the self-limiting character of most cutaneous adverse reactions to CM, the traditional mainstay of treatments follows that of cutaneous adverse reactions to other drugs: withdrawal of the drug and preventative measures for reuse of them, combined with symptomatic treatment.

Severe cutaneous reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESS) may warrant specific therapeutic interventions by a dermatologist.

Search and select criteria

To answer the clinical question a systematic literature analysis was performed.

P (Patients):	patients with late hypersensitivity reaction after contrast media administration;
I (Intervention):	diagnosis, treatment, management, steroid, cyclosporine, topical, emollients;
C (Comparison):	conservative treatment or comparison of interventions above;
O (Outcomes):	recovery, course, outcome, sequels, mortality, morbidity hospitalization.

Relevant outcome measures

The working group considered mortality and recovery critical outcome measures for the decision making process and course, sequel, morbidity and hospitalisation important outcomes for the decision making process.

Methods

The databases Medline (OVID), Embase and the Cochrane Library were searched from 1st of January 1985 to 3th of January 2018 using relevant search terms for systematic reviews (SRs), randomized controlled trials (RCTs) and observational studies (OBS). Search terms are shown under the Tab “Literature Search”. The literature search procured 480 hits: 11 SR, 72 RCTs and 336 OBS. Based on title and abstract a total of 12 studies were selected. After examination of full text all studies were excluded and 0 studies definitely included in the literature summary.

Summary literature

Not applicable. There were no studies investigating the research question.

Conclusions

Not applicable. There were no studies investigating the research question.

Considerations

There are no solid data on different management strategies of late hypersensitivity reactions to CM, especially no studies with a control group.

In many patients there are non-specific symptoms, such as headache, nausea, dizziness, gastro-intestinal upset, mild fever and arm pain (Bellin, 2011; Christiansen, 2000; Egbert, 2014). Skin rashes with erythema and swelling and headache are the most frequent true late hypersensitivity reactions or symptoms (loh, 2010). Most rashes are macular or maculopapular exanthemas, which usually occurs 2-10 days after first exposure to CM and 1 to 2 days after re-exposure to the same CM. Most reactions are mild to moderate in severity, are usually self-limiting and resolve within 1 week.

Treatment is symptomatic, based on the type of reaction presented. More than 90% of the late hypersensitivity reactions involve the skin only. Usually oral antihistamines and topical corticosteroid crèmes or emollients treat these late skin reactions.. Antipyretics may be given for fever, and anti-emetics for nausea or GI symptoms.

Very rarely the patient may develop a severe reaction with generalized pustulosis or blistering of the skin, for which specialized dermatology care needs to be sought (Egbert, 2014).

It seems therefore to be rational to follow the recommendations from the ESUR v10 guideline (Bellin, 2011; ESUR, 2018) and/or the ACR Manual on Contrast Media v10.3 (ACR 2018)

Recommendations

Warn patients who have had a previous hypersensitivity reaction to contrast media, that a late hypersensitivity reaction may be possible, usually a skin reaction.

Patients should contact their general practitioner if they have a late hypersensitivity reaction after CM administration. Consider informing the radiology department about the occurrence and symptoms of a late hypersensitivity reaction after CM administration.

When the symptoms of a late hypersensitivity reaction are mild, a wait-and-see approach can be justified.

Treat late hypersensitivity reactions symptomatically. Consider treatment of skin reactions with oral or topical corticosteroids.

When severe symptoms develop, such as generalized pustulosis or painful cutaneous blisters, refer the patient to a dermatologist.

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Guideline Module Validity And Maintenance

Module[1]	Responsible authors)[2]	Authorisation Year	Next evaluation of validity of guideline	Frequency of evaluation of validity[3]	Who surveys the actuality of this guideline[4]	Relevant factors for changing recommendations[5]
Late reactions	NVvR	2019	2024	5 years	NVvR	New treatment options described and deemed effective

[1] Name of module
[2] Responsible authors (per module)
[3] Time frame: Once every 6 months, year , two years, five years, longer
[4] Responsible scientific society
[5] Variety of reasons: new drugs, new therapies, et cetera

Module 3 Laboratory tests in patients with hypersensitivity reaction to contrast media

Research question

What is the diagnostic value of serum and/or urine testing for contrast media induced hypersensitivity reactions?

Sub questions

1. What is the diagnostic value of tryptase and/or urine (methyl-histamine, methyl-imidazolacetic acid) measurement at the time of the hypersensitivity reaction?
2. What is the diagnostic value of follow-up examination of serum (tryptase) and/or urine (methyl-histamine, methyl-imidazolacetic acid) in order to estimate the risk for a hypersensitivity reaction in the future?
3. What is the diagnostic value of the basophil activation test with contrast media?

Introduction

Serum/blood tests can be performed prior to first contact with the agent, immediately after a reaction and after a possible hypersensitivity reaction in the past.

Hypersensitivity reactions to contrast media are described as acute (immediate) or late (delayed). Reactions occurring within one hour after application of the agents are coined as immediate, reactions occurring later are called delayed. As delayed reactions are considered to be caused by cell-mediated immunity, serum/blood tests so far are only considered relevant to confirm the diagnosis of immediate hypersensitivity. Specific diagnosis of delayed type hypersensitivity can be performed using patch tests and/or in vitro tests such as lymphocyte activation test or other laboratory techniques. The latter tests require specialized laboratories. In order to predict the risk of immediate hypersensitivity reactions serum tests could be aimed at detecting specific antibodies (IgE) to contrast media. In reality this has not been shown to be a realistic option, partly due to technical difficulties.

Moreover, for many years reactions to contrast media were considered as not IgE-driven, although occasionally evidence for an IgE mechanism has been put forward (Carr, 1984; Mita, 1998) In recent years however positive skin tests to contrast media in patients having experienced hypersensitivity reactions have suggested a much larger role for specific IgE, at least in some patients (Clement, 2018). It should be noted however that positive skin tests not necessarily imply an IgE mediated mechanism. The same goes for positive results of the basophil activation test (BAT). Although a positive result of this *in vitro* test usually indicates the presence of specific IgE, it again does not exclude other activation modes of these blood cells. To date there is no commercially available test for directly detecting circulating IgE anti-bodies to contrast media. Application of the BAT to heparin stabilized blood samples of patients shows interesting results but its availability is limited to specialized laboratories. The technique is based on detection of activation of basophils with flow cytometry. CD63 expression serves as a unique marker of identifying activated cells. The technique requires a small amount of fresh blood, less than 0.1 mL. The CD63 marker is located to the same secretory granule that contains histamine, in principle also histamine production could be used as a marker of basophil activation, but determination of histamine is generally more cumbersome than detecting CD63 up regulation (Hoffmann, 2015). Serum tests can also be performed in order to detect a tendency to develop immediate hyper reactivity reactions in general. Serum beta-tryptase (*tryptase*) is an indicator of mast cell activity and can readily be measured in hospital routine laboratories. Serum histamine determination is unpractical because of its short half-life in circulation. An alternative is detection of histamine metabolites in urine. (*N-τ-Methylhistamine*). Although this is a reliable parameter (Keyzer,

1984) very few laboratories have this test in their routine repertoire, and there are not enough data available with respect to contrast media. So, this parameter is not further discussed.

Literature search and selection

To answer our clinical question a systematic literature analysis was performed for the following research question:

> What is the diagnostic value of *serum/blood* testing for contrast media induced hypersensitivity reactions?

P (Patients):	patients with hypersensitivity reactions after undergoing radiological examinations with contrast media;
I (Intervention):	serum tests: tryptase, Blood test, basophil activation test;
C (Comparison):	Clinical diagnosis of hypersensitivity reaction after contrast administration / no serum tests;
R (Reference test):	drug provocation test;
O (Outcomes):	correctly confirmed diagnosis of hypersensitivity reaction to contrast media (sensitivity, specificity, area under the curve, positive predictive value, negative predictive value).

Relevant outcome measures

The working group considered sensitivity and specificity critical outcome measures for the decision-making process; and considered the area under the curve and the positive and negative predictive values important outcome measures.

Search and select (method)

The databases Medline (OVID), Embase and the Cochrane Library were searched from January 1985 to 11th of January 2018 using relevant search terms for systematic reviews (SRs), randomized controlled trials (RCTs) and observational studies (OBS). The literature search resulted in 368 hits: 12 SRs, 17 RCTs and 339 OBS.

Studies were selected based on the following criteria:

- adult patients with hypersensitivity reaction to radio contrast media;
- evaluation of diagnostic properties of serum tests to Contrast Media;
- application of a provocation test to confirm results of cutaneous testing;
- reports predefined outcome measures: sensitivity, specificity, area under the curve, positive predictive value, negative predictive value;
- serum tests tryptase and urine-metabolites should be performed within 24 hours after hypersensitivity reaction;
- no reports of case series or exploratory findings (n≥10).

Based on title and abstract a total of 2 studies were selected. After examination of full text all studies were excluded. Reason for exclusion is reported in exclusion table.

After examination of full text all studies were excluded, and no studies definitely included in the literature summary.

Summary of literature

Not applicable. There were no studies investigating the research question.

Conclusions
Not applicable. There were no studies investigating the research question

Considerations:
Basophil Activation Test
Although no literature was found that answered the search question, a number of studies provide indirect evidence, which will be further discussed here.

Böhm (2011) described that plasma histamine and basophil degranulation using CD63 expression and flow cytometry in blood samples of patients receiving iotrolan (n=12) or iopromide (n=19) injections were analysed before and up to 24 hours after CM injection. In 5 of 12 and 5 of 19 resp. a significant activation of basophils could be measured. No relation with clinical parameters was reported.

Philipse (2012) described a case report where a 28-year old female patient experienced an anaphylactic shock immediately after administration of iomeprol. The reaction was documented by clinical parameters and by an elevation of serum tryptase. Iomeprol induced a dose-dependent CD63 elevation on blood basophils. No activation was shown after stimulation with iohexol and iopromide. CD63 expression on basophils incubated with iomeprol in five controls individuals remained unchanged.

Salas (2013) described a cohort study in which patients with symptoms suggestive of an immediate hypersensitivity reaction to radio contrast media were evaluated with skin tests and a drug provocation test. If skin tests or drug provocation tests were positive a BAT was carried out with the same test panel as used for skin tests. 62.5% of patients considered positive either from skin test or drug provocation test had a positive BAT. The authors suggested that the BAT test could contribute to diagnostic efficacy in patients with hypersensitivity reactions to contrast media. Chirumbolo (2013) responded to the above-mentioned publication (Salas, 2013) that the usefulness of a BAT test is limited due to technical problems in the laboratory and the possibility of delayed reactions to radio contrast media that are likely not to be detected in the BAT test.

Pinnobphun (2011) described a cohort study in which BAT tests were performed in 26 patients with immediate RCM (three different media) reactions and in 43 specimens from healthy volunteers. CD63 and CCR3 positive basophils were analysed by flow cytometry. The BAT test yielded a significantly higher percentage of activated basophils in patients than in normal controls. Both the percentage of activated basophils and the stimulation index had acceptable discrimination powers to diagnose RCM hypersensitivity according to the authors. The specificity of the test ranged from 88.4 to 100%, an ROC curve showed an area under the curve value of 0.79.

Trcka (2008) evaluated 96 patients with anaphylaxis symptoms after contrast media application. In 4 patients (anaphylaxis grade 2 or3) skin test and basophil activation tests suggested an IgE mediated allergy to contrast materials according to the authors. (iopromide, iomeprol, iopentol) Two patients were subsequently treated with an alternative compound that was well tolerated. CD63 and IgE double positive cells assessed the basophil activation. A positive response was dependant on an analysis of more than 5% activated basophils, provided a stimulation index equal or higher than 2.

Kolenda (2017) evaluated the value of BAT and skin test for the diagnosis of RCM hypersensitivity. Thirty-three patients had responded to an injection of GBCA during MRI.

Skin test were performed according to EAACI–ENDA guidelines. BAT was performed using the Allergenicity kit (Beckman Coulter). Gadobenate, gadoteric acid and gadobutrol were analysed in three tenfold dilutions. Patients were considered as 'non allergic' when their skin tests were negative whereas they were considered 'allergic' when the skin tests were positive with an evocative clinical history. CD 203C expression induced in more than 6% of the basophil cells was considered as a positive response. In 13 of the 14 non-allergic patients the BAT was negative, corresponding to a specificity of 93%. When re-exposed five of 14 patients tolerated the culprit drug confirming the 'non-allergic' nature of the primary reaction. In the 'allergic' population BAT was positive in 13 of 19 for the pulled GBCA, sensitivity of 68%.

In conclusion:
To date four clinical studies, a case report and a mechanistic study have been published concerning application of the BAT in patients with hypersensitivity reactions to contrast media. Based on 3 studies two review articles concluded that: the literature demonstrated a sensitivity of 46 to 63% and specificity is of 89 to 100% (Mangodt, 2015; Steiner, 2016). This conclusion however bypasses heterogeneity in laboratory techniques, control groups and agents involved. It should be noted that these estimates of sensitivity and specificity were based on a low percentage of clinical reactors as were identified as hypersensitive by skin test or drug provocation tests. However, in the recent study of Kolenda almost half of the patients that had responded with symptoms within minutes after GBCA injections had positive skin tests (performed according the EAACI–ENDA guidelines). In these patients a high specificity and relatively high sensitivity was found.

Based on the earlier three studies, performing the BAT test in all patients with a history of hypersensitivity reactions to contrast media would probably only identify a very low percentage as 'allergic'. However recent studies report a higher percentage of skin test positive patients. The diagnostic value of both skin testing and the BAT are dependent on studies with adequate power and an objective outcome parameter such as a graded dose challenge.

Serum Tryptase
Although no literature was found that answered the search question, a number of studies provide indirect evidence, which will be further discussed here.

Zhai (2017) described a cohort study in 27 adult patients presenting with at least a grade 2 immediate reaction after intravenous injection of ICM during CT. Blood samples were evaluated with multiple parameters. Tryptase levels were significantly elevated as compared to a control group of healthy adults

Clement (2018) reported a cohort study in 245 patients with a history of hypersensitivity who were skin tested, of whom 41 were identified as 'allergic' to iodinated agents and 10 to gadolinium based ones. Histamine and tryptase concentrations increased with the severity of the reaction.

Comment (2014) described a cohort study where in the realm of forensic pathology beta tryptase measurements for diagnostic purposes were performed in post-mortem serum obtained from femoral blood in 94 patient with different fatalities, among others death following contrast material administration (six cases). Values over 11.4 ng/mL were systematically identified in serum and pericardial fluid following contrast material anaphylaxis and in six cases unrelated to anaphylaxis.

Fellinger (2014) described that a cohort of 15298 individuals was tested for basal tryptase levels. Elevated serum tryptase (> 11.4 ng/mL, mean 20+/- 21 ng/mL) as a predictor of anaphylaxis was evaluated in 900 patients and compared to 900 patients with normal tryptase values. Elevated tryptase levels were significantly associated with adverse reactions to drugs, radio contrast media and insect sting reactions. Anaphylaxis was more common in patients with elevated tryptase levels.

Srivastava (2014) reported a systemic retrospective survey that was carried out in 171 individuals whose data were extracted from the emergency department and specialist allergy clinic records. Thirty-four patients had a grade 1 anaphylaxis reaction, 61 a grade 2 reaction, 27 a grade 3 reaction and six patients a grade 4 reaction. 24 patients could not be graded due to lack of adequate clinical details, 6 patients developed a biphasic response. 50% of cases were diagnosed with idiopathic systemic anaphylaxis and 28% triggered by drugs, foods, and other allergies. Serial tryptase measurements were not available in 117 of the cohort. A weak positive correlation was detected between acute serum tryptase and severity.

Palmiere (2014) performed a retrospective literature analysis on risk factors of causes of anaphylaxis due to contrast media. Moreover, fatal cases investigated in the author's own institution was evaluated. Only a minority of fatal cases had been previously exposed to contrast compounds. In eight cases with fatal anaphylaxis, post-mortem serum tryptase concentrations ranged from 51 to 979 ng/mL.

In conclusion:
Tryptase is the principal protein component of human mast cell secretory granules.
It was shown to be a marker of mast cell degranulation that is released together with histamine. Detecting elevated levels of tryptase following a suspected hypersensitivity reaction may help to establish the final diagnosis of anaphylaxis. Tryptase levels peak at 0.5 to 1.5 hours and thereafter rapidly decline with a 1.5-2.5 hours half-life (Schwartz, 2006).

The ESUR guidelines suggest that: blood samples for tryptase are taken following suspected anaphylaxis, so that the diagnosis can be established. The minimum recommendation is one sample 1 to 2 hours after the reaction point. Ideally three samples should be obtained, the first one once this visitation is underway the second at 1 to 2 hours after the reaction and the third at 24 hours or during convalescence (ESUR v10)

An elevated level of tryptase is also a hallmark of systemic mastocytosis. Systemic mastocytosis is a risk factor for developing hypersensitivity reactions to multiple agents such as insect venom and drugs that tend to cause mast cell degranulation (ESUR v10). Contrast agents, notably iodinated products, may per se cause some extent of mast cell and/or basophil degranulation. However, the risk of modern contrast agents in mastocytosis seems to be limited (Hermans, 2017). Moreover, since mastocytosis is a rare disease, routine determination of tryptase does not seem warranted, notably not when other signs and symptoms of mastocytosis are absent (urticaria pigmentosa, osteoporosis at early age, insect sting and/or unexplained anaphylactic reactions).

When confronted with a patient responding with a presumed hypersensitivity reaction to infusion of contrast media the first care of course should be for the safety of the patient. However, once the patient is stabilized care should be taken that clinical parameters are documented according to standard procedures. These procedures include exact documentation of infusion materials, medication taken by the patient or given during the

procedure and clinical parameters such as such as blood pressure, heart rate, oxygen saturation, auscultation of the lungs, inspection of the oral cavity and of the skin of the patient.

The signs and symptoms of hypersensitivity reactions are not always clear-cut or may be misleading initially. Therefore, objective documentation is sought for. Tryptase is a readily available marker for mast cell/basophil activation; serum levels are normally less than 11.5 ng/mL. Other studies have proposed a somewhat higher cut-off value (14 ng/mL). Elevated levels of serum tryptase occur in both anaphylactic and anaphylactoid (non IgE-mediated) reactions, but a negative test does not fully exclude anaphylaxis. Basal tryptase levels over 20 µg/L are suggestive of systemic mastocytosis. The utility of serum tryptase for the diagnosis of anaphylaxis has been published in the context of the NICE quality standard anaphylaxis 2016 (NICE QS119).

Serum tests in patients suspected of having experienced hypersensitivity reactions to contrast media in the past

Conclusions:

Laboratory tests aimed at detecting specific antibodies can be performed by using skin tests and/or an in vitro basophil activation test (BAT) with the suspected compound. In many cases it is not clear to which compound the patient has reacted in the past. Both skin testing and the BAT test may help to select an agent for future safe use. However, the diagnostic accuracy of these methods still is insufficiently documented. The final evaluation of the diagnostic power of these tests is dependent on the comparison with a 'golden standard', probably the graded dose challenge.

Concerning the documentation of hypersensitivity reactions to contrast media (grade II and III) patients should be followed up with at least one sample for blood tryptase 1 to 2 hours after the reaction and one at a later time point (ESUR v10).

Testing of baseline levels of tryptase before contrast studies are performed may be useful in patients who have previously developed hypersensitivity reactions to contrast media. Elevated baseline levels of serum tryptase in a steady state situation suggest the presence of a mast cell disorder. Already mildly elevated baseline tryptase levels somewhat increase the risk of anaphylaxis (Fellinger). Indolent systemic mastocytosis (ISM) is considered a risk factor for contrast agent anaphylaxis, but a recent study did not confirm this (Hermans, 2017). ISM is the most frequent form of mast cell disorders; its prevalence in the Netherlands is suggested to be around 1 in 10,000.

Detection of serum tryptase is relatively cheap, routinely performed in many laboratories, serum samples can be stored at -20°C and normal values are well established. If elevated baseline tryptase values are found (>20 µg/L) a further haematological analysis should be performed including C-kit analysis to further specify the type of mast cell disease.

Given the low frequency of hypersensitivity reactions to contrast agents, the low frequency of mastocytosis in the population and the still insufficiently documented sensitivity and specificity of serum tests (incl. BAT), routine testing of all patients prior to injection of contrast agents is not warranted.

It is important to have local protocols that describe which physician is responsible for measuring the tryptase levels during and after a hypersensitivity reaction (see Chapter Organisation of healthcare).

Recommendations

Do not perform a Basophil Activation Test routinely in all patients with a history of hypersensitivity reactions receiving contrast medium.

Measure serum tryptase between 1 to 2 hours from the start of all moderately severe to severe acute hypersensitivity reactions to contrast media.

When tryptase is elevated, refer the patient to a drug allergy specialist.

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Validity and updating

Module[1]	Control holder(s)[2]	Year of authorisation	Next assessment actuality guideline[3]	Frequency of assessing actuality[4]	Who monitors actuality[5]	Relevant factors for changes in recommendations[6]
Laboratory tests	NVvR	2019	2024	5 years	NVvR	New tests or new information on diagnostic parameters of tests available

[1] Name of module
[2] Responsible authors (per module)
[3] Year in which the guideline should be assessed for updating
[4] Time frame: Once every 6 months, one year, two years, five years, or longer
[5] Responsible scientific society
[6] Variety of reasons: new drugs, new therapies, et cetera

Module 4 Diagnostic value of skin testing for hypersensitivity reactions to contrast media

Question

What is the diagnostic value of skin testing for hypersensitivity reactions to contrast media?

Introduction

Hypersensitivity reactions to contrast media (CM) have traditionally been classified as non-allergic reactions, and skin tests have been regarded as inappropriate tools in patients having experienced such reactions. However, during the last few years several investigators have reported positive skin tests in patients with both immediate and non-immediate hypersensitivity reactions after CM exposure, which indicates that immunological mechanisms may be involved much more frequently. In this chapter the diagnostic value of cutaneous tests for CM hypersensitivity reactions is assessed, which may serve as a more valid alternative to prophylactic medication for CM reactions. Furthermore, the working group evaluates whether these skin tests should be recommended in clinical practice, and under which conditions.

Literature search and selection

To answer our clinical question a systematic literature analysis was performed for the following research question:

What is the diagnostic value of cutaneous testing for hypersensitivity reactions to contrast media?

P (patient category):	patients with hypersensitivity reactions after radiological examinations with contrast media;
I (intervention):	cutaneous tests: skin test, patch test (PT), Intradermal test (IDT), skin prick test (SPT) or scratch test;
C (comparison)	clinical diagnosis of hypersensitivity reaction after contrast administration;
R (Reference)	drug provocation test;
O (outcome)	correctly confirmed diagnosis of hypersensitivity reaction to contrast media (sensitivity, specificity, area under the curve, positive predictive value, negative predictive value).

Relevant outcome measures

The working group considered sensitivity and specificity critical outcome measures for the decision-making process; and considered the area under the curve and the positive and negative predictive values important outcome measures.

Search and select (method)

The databases Medline (OVID), Embase and the Cochrane Library were searched from January 1985 to 4th of January 2018 using relevant search terms for systematic reviews (SRs), randomized controlled trials (RCTs) and observational studies (OBS). The literature search resulted in 358 hits: 7 SRs, 33 RCTs and 318 OBS.

Studies were selected based on the following criteria:

- adult patients with hypersensitivity reaction to contrast media;
- evaluation of diagnostic properties of cutaneous tests to contrast media;
- application of a provocation test to confirm results of cutaneous testing;

- reports predefined outcome measures: sensitivity, specificity, area under the curve, positive predictive value, negative predictive value;
- no reports of case series or exploratory findings (n ≥ 10).

Based on title and abstract a total of 37 studies were selected. After examination of full text a total of 33 studies were excluded and five studies were definitely included in the literature summary. Reason for exclusion is reported in exclusion table.”). Cross-referencing leads to the inclusion of one additional study.

Five studies were included in the literature analysis; the most important study characteristics and results were included in the evidence tables. The evidence tables and assessment of individual study quality are included. Since study setup, and applied cutaneous tests differed across the studies, we were not able to pool the outcome of the diagnostic test properties.

A total of 13 studies did not fulfil the predefined selection criteria, but described the positive rates of cutaneous tests in patients that had a hypersensitivity reaction after CM administration. The positive rates in these studies are also described under *Positive rates of cutaneous tests*. Because these studies did not fulfil the selection criteria, and did not include a comparison to a reference test, only descriptive data of these studies was shown, and evidence tables and risk of bias tables of these studies are not included.

Summary of the literature

1. Skin testing for acute (immediate) hypersensitivity reactions to contrast media

The diagnostic properties of cutaneous tests for acute (immediate) hypersensitivity reactions (HSR) to Contrast Media (CM) were evaluated in 4 studies (Caimmi, 2010; Kim, 2013; Salas, 2013; Sesé, 2016).

Caimmi (2010) studied 159 patients. Patients were tested with the culprit iodine-based contrast medium (ICM) and a set of other ICM if they were positive for the culprit ICM or if its name was unknown. In order to know which ICM was involved, either patients already knew which drug had supposedly caused the reaction and provided us the name, or we contacted the hospital in which the reaction had occurred. The ICM used were: amidotrizoate, ioxithalamate, iopamidol, iohexol, ioversol, iopromide, iomeprol, iobitridol, iodixanol and ioxaglate. Skin tests were performed firstly as prick tests with the undiluted commercially available solution and then, if negative, by intradermal tests (IDT) at a 1: 10 dilution. Prick tests were considered positive if, after 15 min, the size of the weal was at least 3 mm in diameter. For IDT, positivity was considered when the size of the initial weal increased by at least 3 mm in diameter after 15 to 20 min, considering as non-irritant a maximum dilution of 1/10. The negative predictive value was defined as the proportion of patients with negative skin test results to at least one ICM at first testing who had a further injection with that ICM without reacting. One hundred participated (75.5% participation rate). Seventy-one of them (5 9.2%) were females of a median age of 56 (45–65) years. The majority of the reactions were immediate (101 out of 120, 84.2%), and in two cases, it was not possible to assess whether the reaction was immediate or non-immediate. For immediate reactions, 42 (41.6%) were of grade 1, 34 (33.7%) of grade 2, 20 (19.8%) of grades 3 and five (4.9%) of grade 4. Only one (5.9%) of the 17 non-immediate reactions was moderate, all the others were mild (16 to 94.1%).

Kim (2013) retrospectively included 1048 patients. The mean (SD) age was 55.1 (14.5) years; 501 (47.8%) were male. Intradermal test with the RCM that was to be used in the

pending nonionic CM-enhanced CT was performed just before the CT examinations. The nonionic CM used in our contrast CT scans was iopromide, iomeprol, iohexol, and iodixanol. Intradermal tests were conducted on the volar surface of the forearm with a negative control, saline. A 1:10 solution of contrast medium (0.03 to 0.05 mL), which has been accepted as a non-irritating concentration, was gently injected into the skin to produce a small superficial bleb of 2 to 4 mm. Skin test positivity was determined when the diameter of the wheal increased by at least 3 mm, and surrounding erythema was observed after 15 to 20 minutes. If a patient had a negative response to skin tests, CT was performed as scheduled (provocation). Of the 376 patients previously exposed to CM, 61 (16.2%) had a history of at least 1 mild CM-associated reaction: 56 (91.8%) had immediate and 5 (8.2%) non-immediate reactions.

Salas (2013) included 90 patients with a history of immediate HSR after contrast media (CM). Immediate HSR was classified according to the Ring and Messmer scale.

Skin Test (ST) was carried out using the following CM: iobitridol, iomeprol, iodixanol, iohexol, ioversol, iopromide and ioxaglate. Prick tests were performed using undiluted CM and IDT using 10-fold dilutions. In those with a negative ST, a single-blind placebo-controlled provocation test was performed with the CM involved, as described. In patients with a positive ST and/or provocation test, a basophil activation test (BAT) was performed with iohexol (3; 0.3 mg/ml), iodixanol (3; 0.3 mg/ml), iomeprol (3.5; 0.35 mg/ml) and ioxaglate (5.8; 0.58 mg/ml) (based on dose–response curves and cytotoxicity studies). The median age of the subjects evaluated was 54.50 ± 27 years; 63 (60%) were women. The CM involved in the reaction was iomeprol in 26 cases (28.89%), iodixanol in 19 (21.11%), iohexol in 11 (12.22%), iopromide in 9 (10.00%) and unknown in 25 (27.78%). According to the clinical history, most cases developed reactions with skin involvement (65.65% urticaria/ angioedema and 30% generalized erythema), and only 4.44% had airway or cardiovascular involvement. Regarding symptom severity, 69 cases (76.71%) had grade I reactions, 18 (20%) grade II and 3 (3.33%) grade III. No patients had grade IV reactions.

Sesé (2016) included 37 patients with a definite history of immediate HSR due to Iodine-based Contrast Media (ICM). Immediate HSR was classified according to the Ring and Messmer scale. Skin tests were performed at least 6 weeks after the HSR on the volar forearm with the suspected ICM and with four other ICM. Skin prick tests (SPTs) involved freshly prepared undiluted ICM commercial solutions, and intradermal tests (IDTs) were performed successively with 100-fold and then 10-fold solution diluted in 0.9% sterile saline. Saline and chlorhydrate histamine were negative and positive controls, respectively. In total, 37 patients (24 women, mean age 49.3 years at the time of the reaction) completed the tests. The clinical severity of the reaction was grade I for 26 (70%), grade II for 4 (11%), and grade III for 7 (19%); 35 (95%) reported skin or mucosal symptoms, including pruritus (n = 11), facial erythema (n = 6), generalized erythema (n = 20), urticaria (n = 7), and angioedema (n = 5).

2. Skin testing for late (delayed) hypersensitivity reactions to contrast media

The diagnostic property of cutaneous tests for late (non-immediate) hypersensitivity reactions (HSR) to Iodinated Contrast Media (ICM) was evaluated in one study (Torres, 2012). Torres included a total of 161 subjects with a history of a non-immediate reaction imputable to at least one CM was evaluated. One patient who developed Stevens–Johnson syndrome was not included. The median age was 58.5 years (IR: 48.85 to 66.5) with 82 men (50.9%). According to the information obtained from the clinical history, the CM involved in the reaction were iomeprol in 53 (32.9%), iodixanol in 46 (28.6%), iohexol in 27 (16.8%),

iobitridol in 4 (2.5%), ioversol in 3 (1.9%), iopromide in 3 (1.9%), ioxaglate in 2 (1.2%) and unknown in 23 (14.3%). According to the clinical history, 108 cases (67.1%) developed symptoms compatible with exanthema and 53 (32.9%) with delayed urticaria. Regarding symptom severity, 16 cases (9.9%) had mild reactions, 143 (88.8%) moderate reactions, and 2 severe reactions (1.2%) consisting of desquamative exanthema. Concerning the number of episodes, 132 cases (82%) had one episode and 29 cases (18%) two episodes.

Results

1. Skin testing for acute hypersensitivity reactions

Negative predictive value

The rate of a positive skin test in the study of Sesé (2016) was 13.5% (95% CI 4 to 29%) and increased to 20% (95% CI 4 to 48%) for patients who consulted during the year after the HSR. Among the 32 patients with negative skin test results, 31 were challenged successfully, 15 with the culprit ICM. One grade I reaction occurred 2 h after challenge (generalized pruritus, erythema, and eyelid oedema lasting < 1 h) and was considered a positive intravenous challenge result. At 2 h after provocation test, two patients reported generalized and isolated pruritus that regressed with antihistamine therapy and was not considered a positive IPT result. None of five patients with positive skin test to ICM were re-exposed to contrast media during radiologic examination, positive predictive could not be calculated. For an immediate HSR to ICM, the negative predictive value for skin tests with low dose was 80% (95% CI 44 to 97%).

Kim (2013) showed that among the 1046 patients who had negative responses on skin tests, 52 (5.0%) showed immediate-type adverse reactions after CT using radio contrast media. However, most reactions were mild and cutaneous, such as pruritus, urticaria, and mild angioedema. Only 1 patient (0.1%) had a grade II moderate immediate reaction accompanied by breathing difficulty and mild laryngeal oedema, which were relieved with an antihistamine. The negative predictive value of the pre-screening skin test for immediate hypersensitivity reactions before contrast media administration was 95.0%. The negative predictive value of the skin test for immediate hypersensitivity reactions in patients with a history of contrast media hypersensitivity reactions was 80.3% (n= 49/61) and that in patients without a history was 95.9% (n= 945/985).

Results of Salas (2013) showed that five subjects (5.56%) had a positive skin test: three by prick test (one to iodixanol, one to iomeprol and one to iohexol) and five by intradermal testing (four to iohexol, three iodixanol and two to iomeprol). In cases with a negative skin test to all CM tested (N = 74), provocation test was carried out with the culprit CM if known, being positive in three cases; one to iodixanol, one to iomeprol and one to iodixanol, iohexol plus iomeprol. In total, 11 patients with a negative ST refused to undergo a provocation test, resulting in a negative predictive value to immediate hypersensitivity reactions of 95.26%. Eight (8.9%) cases were confirmed as having IHR, 5 (62.5%) by ST and 3 (37.5%) by provocation test. Five from those confirmed as IHR (62.5%) had a positive BAT.

The results of Caimmi (2010) revealed that ICM skin tests were positive in 21 patients (17.5%). Seventeen of them (80.9%) had a history of immediate reaction (four with grade 1, eight grade 2, four grade 3 and one grade 4). Prick tests were all negative. IDT were positive at 20 min for 15 patients with an immediate history and for the patient with unknown chronology. Caimmi (2010) found one single false negative; the negative predictive value of ICM skin tests was 96.6% (95% CI: 89.9 to 103.2).

Quality of evidence
The quality of certainty of evidence was graded as very low due to high risk of bias (see Tab Rob assessment, downgraded by two points) and low number of patients (imprecision downgraded by one point).

2. Skin testing for delayed hypersensitivity reactions

Negative predictive value

In the total group of cases evaluated (N = 161), 34 subjects (21.1%) developed a delayed reading of the intradermal tests positive (13 at 1/10 dilution and 29 undiluted). Of these, 27 were skin-test positive to just one CM, 6 to two CM and 1 to three. The immediate reading of the intradermal tests was negative in all cases. The skin test was positive to iomeprol in 21 cases (50%), to iodixanol in 7 (16.7%), to iobitridol in 5 (11.9%), to ioxaglate in 4 (9.5%), to iohexol in 3 (7.1%) and to iopromide in 1 (2.4%). In the 34 cases with a positive intradermal test, 10 also had a positive patch test. No positive patch tests were detected in the patients with negative intradermal results. In the patients with a negative skin test to all the CM tested (N = 127), a provocation test was carried out with the CM involved. Provocation test was positive in 44 cases (34.6%), 19 to one CM and 3 to two CM. Thirty-eight cases (76%) were positive to iodixanol, 8 (16%) to iomeprol and 4 (8%) to iohexol. The time interval between administration and symptom development was: 1 to 6 h (13 cases), 7 to 12 h (27 cases), 13 to 24 h (68 cases), 25 to 48 h (41 cases) and > 48 h (12 cases).

Quality of evidence
The quality of certainty of evidence was graded as very low due to high risk of bias (see Tab Rob assessment, downgraded by two points) and low number of patients (imprecision downgraded by one point).

Literature conclusions

Acute Hypersensitivity Reactions: Negative Predictive value

Very Low GRADE	The negative predictive value of the cutaneous test is estimated to be 80 to 97%. The sensitivity and specificity for the cutaneous test for immediate hypersensitivity reaction to contrast media is unknown in patients suspected of contrast media hypersensitivity. *Sources: (Caimmi, 2010; Kim, 2013; Salas, 2013; Sesé, 2016)*

Late Hypersensitivity Reactions: Negative Predictive value

Very Low GRADE	The negative predictive value of the cutaneous test is estimated to be 65%. The sensitivity and specificity for the cutaneous test for non-immediate hypersensitivity reaction to contrast media is unknown in patients suspected of contrast media hypersensitivity. *Sources: (Torres, 2012)*

Positive rates of cutaneous tests

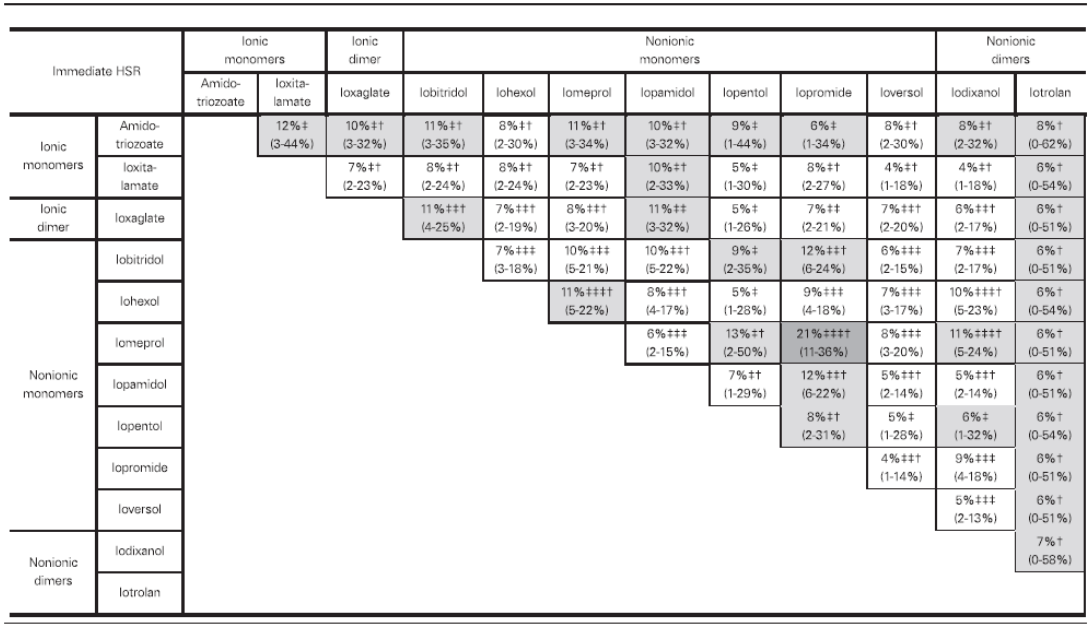
The positive rate of cutaneous tests was reported in 12 studies. Since these studies do not compare cutaneous tests with a provocation test, they are not in line with the PICO. However, studies on positive rates of skin tests in patients with HSR to ICM contain important clinical information. Therefore, we have additionally synthesized literature evaluating positive rates of cutaneous tests in patients with HSR to ICM. Since these studies do not describe comparative research, we did not create risk of bias and evidence tables for these studies.

In patients with immediate HSR to ICM, the pooled positive rate of skin tests was 17% (95% CI, 11–26%; I^2= 45%) and was identical to that of IDT (Table 4.1). The pooled positive rate of SPTs was 3% (95%CI= (1-5%); I^2= 0%). The pooled positive rates of IDT were shown to rise as the severity of reactions increased: pooled positive rate for mild HSR is 12% (95%CI= (6 to 23%); I^2= 38%); moderate HSR 16% (95%CI= (10 to 24%); I^2 = 6%) and for severe HSR, 52% (95%CI= (31 to 74%), I^2= 42%). Table 4.1 presents a detailed overview of positive rates across studies. Figure 4.2 presents an overview of per-test cross-reactivity rates between pairs of ICM in skin test positive patients with HSR to ICM.

Table 4.1 Positive rates of cutaneous tests in patients with immediate HSR to ICM

		Positive rate of skin tests, %		Test Site		Positive rate of IDT, % Severity of HSR		
		SPT[a]	IDT[b]	SPT[a]	IDT[b]	Mild	Moderate	Severe
Dewachter, 2001	ICM[c]	50 (2/4)	100 (4/4)	Forearm	Back	-	-	100 (4/4)
Trcka, 2008	ICM[c]	-	4 (4/96)	Not specified	Not specified	0 (0/40)	7 (3/44)	8 (1/12)
Brockow, 2009	ICM[c]	3 (4/122)	26 (32/121)	Forearm	Forearm	26 (24/92)	-	28 (8/29)
Caimmi, 2010	ICM[c]	0 (0/101)	15 (15/101)	Not specified	Not specified	-	-	-
Dewachter, 2011	ICM[c]	4 (1/24)	46 (12/26)	Forearm	Back	33 (3/9)	40 (4/10)	71 (5/7)
Goksel, 2011	ICM[c]	0 (0/14)	14 (2/14)	Forearm	Forearm	14 (1/7)	14 (1/7)	-
Pinnobphun, 2011	ICM[c]	0 (0/63)	24 (15/63)	Not specified	Not specified	23 (12/53)	0 (0/5)	60 (3/5)
Kim, 2013	ICM[c]	3 (1/32)	26 (12/46)	Not specified	Forearm	13 (4/31)	25 (2/8)	57 (4/7)
Kim, 2014	ICM[c]	2 (1/51)	65 (33/51)	Forearm	Forearm	-	18 (2/11)	78 (31/40)
Renaudin, 2013	ICM[c]	14 (1/7)	57 (4/7)	Not specified	Not specified	-	-	57 (4/7)
Prieto-Garcia, 2013	ICM[c]	0 (0/106)	10 (11/106)	Not specified	Not specified	9 (6/66)	14 (4/29)	9 (1/11)
Salas, 2013	ICM[c]	3 (3/90)	6 (5/90)	Not specified	Forearm	0 (0/69)	11 (2/18)	100 (3/3)
Sesé, 2016	ICM[c]	3 (1/37)	13.5% (5/37)	Forearm	Not specified	11 (4/37)	3 (1/37)	

[a]SPT = Skin Prick Test; [b]IDT= Intradermal Test; [c]Iodine-based Contrast Media



Immediate HSR		Ionic monomers		Ionic dimer	Nonionic monomers							Nonionic dimers	
		Amido-triozoate	Ioxita-lamate	Ioxaglate	Iobitridol	Iohexol	Iomeprol	Iopamidol	Iopentol	Iopromide	Ioversol	Iodixanol	Iotrolan
Ionic monomers	Amido-triozoate		12%‡ (3-44%)	10%‡† (3-32%)	11%‡† (3-35%)	8%‡† (2-30%)	11%‡† (3-34%)	10%‡† (3-32%)	9%‡ (1-44%)	6%‡ (1-34%)	8%‡† (2-30%)	8%‡† (2-32%)	8%† (0-62%)
	Ioxita-lamate			7%‡† (2-23%)	8%‡† (2-24%)	8%‡† (2-24%)	7%‡† (2-23%)	10%‡† (2-33%)	5%‡ (1-30%)	8%‡† (2-27%)	4%‡† (1-18%)	4%‡† (1-18%)	6%† (0-54%)
Ionic dimer	Ioxaglate				11%‡‡† (4-25%)	7%‡‡† (2-19%)	8%‡‡† (3-20%)	11%‡‡ (3-32%)	5%‡ (1-26%)	7%‡‡ (2-21%)	7%‡‡† (2-20%)	6%‡‡† (2-17%)	6%† (0-51%)
Nonionic monomers	Iobitridol					7%‡‡‡ (3-18%)	10%‡‡‡ (5-21%)	10%‡‡† (5-22%)	9%‡ (2-35%)	12%‡‡† (6-24%)	6%‡‡‡ (2-15%)	7%‡‡‡ (2-17%)	6%† (0-51%)
	Iohexol						11%‡‡‡† (5-22%)	8%‡‡† (4-17%)	5%‡ (1-28%)	9%‡‡‡ (4-18%)	7%‡‡‡ (3-17%)	10%‡‡‡† (5-23%)	6%† (0-54%)
	Iomeprol							6%‡‡‡ (2-15%)	13%‡† (2-50%)	21%‡‡‡† (11-36%)	8%‡‡‡ (3-20%)	11%‡‡‡† (5-24%)	6%† (0-51%)
	Iopamidol								7%‡† (1-29%)	12%‡‡† (6-22%)	5%‡‡† (2-14%)	5%‡‡† (2-14%)	6%† (0-51%)
	Iopentol									8%‡† (2-31%)	5%‡ (1-28%)	6%‡ (1-32%)	6%† (0-54%)
	Iopromide										4%‡‡† (1-14%)	9%‡‡‡ (4-18%)	6%† (0-51%)
	Ioversol											5%‡‡‡ (2-13%)	6%† (0-51%)
Nonionic dimers	Iodixanol												7%† (0-58%)
	Iotrolan												

Figure 4.2 Cross-reactivity rates between pairs of ICM in skin test-positive patients with HSR to ICM. (from meta-analysis Yoon et al. Allergy 2015)
Cross-reactivity was extracted based on the results of intradermal test with 10^{-1} diluted ICM and patch test with undiluted ICM. If available, results of drug provocation test and graded challenge were also used. The number of † is the number of pooled studies. Pooled cross-reactivity rate is categorized and expressed in grey scale: white, pooled point estimate is ≤10%, and its upper limit of 95% CI is ≤30%; light grey, pooled point estimate is 11% and 15%, or pooled point estimate is ≤10 with its upper limit of 95% CI is >30%; grey, pooled point estimate ranged from 16% and 25%; dark grey, pooled point estimate ranged from 26% and 50%.

HSR, hypersensitivity reaction; ICM, iodinated contrast media; CI, confidence interval.

Considerations
As hypersensitivity reactions to CM have traditionally been classified as non-allergic reactions, skin tests have been regarded as inappropriate tools in patients having experienced such reactions. However, increasing evidence suggests that immunological mechanisms may be involved in CM-induced hypersensitivity reactions to a much larger degree, partly based on the positive skin tests in patients with both immediate and nonimmediate hypersensitivity reactions after CM exposure.

Implementing the results of skin tests might be a more valid alternative to prophylactic medication for prevention of the recurrence of CM reactions (Rosado Ingelmo, 2016). Skin tests have good sensitivity when performed within 6 months after the hypersensitivity reaction. After this time, sensitivity decreases. Therefor a speedy referral to a drug allergy specialist is recommended.

Few studies were found that met the inclusion criteria and were all with iodinated contrast media. Even though, no hard evidence is available on skin testing for gadolinium based CA, the hypersensitivity reactions are more often IgE-mediated in reactions after gadolinium-based CA and very similar in symptomatology to hypersensitivity reactions after iodine-based CM and therefore it seems logical to extend skin testing to hypersensitivity reactions to all CM (Clement, 2018).

Since included studies were considerable heterogeneous regarding to study setup and applied skin tests, no pooled outcomes of diagnostic test properties could be assessed which limits the recommendations that can be made on the current literature study.

If a previous reaction had shown a delayed cutaneous response it is unknown if premedication and or skin testing would reduce the risk of subsequent reactions. Delayed skin reactions may be life threatening notably when blistering has occurred. Skin testing in such cases may not be safe.

Performing and Reporting Skin Testing for Contrast Media
Most hospitals nowadays have contracts with just a few contrast media vendors. For skin testing of contrast media, however, it is important to test a panel of contrast agents (ICM and/or GBCA), including the culprit contrast agent and potential alternatives. Such a panel could be individualized for the specific hospital (group) where the patient comes from.

In order to facilitate establishment of such a local panel of iodine-based and gadolinium-based agents for allergologic skin testing, we have listed the available agents in The Netherlands and their indications below.

(See for physicochemical characteristics of GBCA also Table 1 in the Introduction to Safe Use of Gadolinium).

Table 4.3 Contrast agents in The Netherlands registered with the Medicine Evaluation Board

Iodine-based contrast media			
Name	*Commercial Name*	*Company*	*Main Indication*
Iopromide	Ultravist	Bayer Healthcare	Intravascular CT/Angio
Iopamidol	Iopamiro	Bracco Imaging	Intravascular CT/Angio
Iomeprol	Iomeron	Bracco Imaging	Intravascular CT/Angio
Iohexol	Omnipaque	GE Healthcare	Intravascular CT/Angio
Iodixanol	Visipaque	GE Healthcare	Intravascular CT/Angio
Ioversol	Optiray	Guerbet	Intravascular CT/Angio
Iobitridol	Xenetix	Guerbet	Intravascular CT/Angio

Amidotrizoate meglumine	Gastrografine	Bayer Healthcare	Gastrointestinal RF/CT
Iopamidol	Gastromiro	Bracco Imaging	Gastrointestinal RF/CT
Ioxithalamate meglumine	Telebrix Gastro	Guerbet	Gastrointestinal RF/CT

Gadolinium-based contrast agents			
Name	*Commercial Name*	*Company*	*Allowed Indication*
Gadobutrol	Gadovist	Bayer Healthcare	Total Body MRI
Gadoteridol	ProHance	Bracco Imaging	Total Body MRI
Gadoterate meglumine	Dotarem/Artirem	Guerbet	Total Body MRI
	Clariscan	GE Healthcare	Total Body MRI
	Dotagraf	Bayer Healthcare	Total Body MRI
Gadoxetate disodium	Primovist	Bayer Healthcare	Liver MRI
Gadobenate dimeglumine	MultiHance	Bracco Imaging	Liver MRI
Gadopentetate meglumine	Magnevist	Bayer Healthcare	MR Arthrography

See also: https://www.geneesmiddeleninformatiebank.nl/nl/

When reporting skin tests, it is optimal that the allergologist gives a clear written recommendation in the electronic patient dossier about:
1) The possible ICM and/or GBCA that can be used in future CM-enhanced studies
2) The use of or need for premedication in future CM-enhanced studies

Recommendations

Do not perform skin tests routinely after every hypersensitivity reaction to a contrast medium.

Refer the patient to a specialist in drug allergy to perform skin tests within 6 months after the hypersensitivity reaction in the following patient groups:
- Severe hypersensitivity reactions to a contrast medium.
- Hypersensitivity reactions with increased tryptase levels.
- Hypersensitivity reactions to 2 or more different contrast media of the same type (for example 2 different iodine-based CM) or to 2 or more types of contrast media (for example iodine-based CM and gadolinium-based CA).

Specify the used contrast agent in the referral.

Refer the patient to a specialist in drug allergy to perform skin tests in all patients with breakthrough hypersensitivity reactions despite premedication with corticosteroids and H1-antihistamines.

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Validity and updating

Module[1]	Control holder(s)[2]	Year of authorisation	Next assessment actuality guideline[3]	Frequency of assessing actuality[4]	Who monitors actuality[5]	Relevant factors for changes in recommendations[6]
Cutaneous tests	NVvR	2019	2024	5 years	NVvR	New tests or new information on diagnostic parameters of tests available

[1] Name of module
[2] Responsible authors (per module)
[3] Year in which the guideline should be assessed for updating
[4] Time frame: Once every 6 months, one year, two years, five years, or longer
[5] Responsible scientific society
[6] Variety of reasons: new drugs, new therapies, et cetera

Module 5 Prophylaxis of hypersensitivity reactions after contrast administration

Clinical Question

Which prophylactic measures should be taken in patients with increased risk of hypersensitivity reactions after contrast administration?

Introduction

Patients report hypersensitivity reactions to contrast media, and often these have occurred in the past. This can involve objective signs or symptoms that fit well with a hypersensitivity reaction. However, in many cases other complaints are reported, such as hyperventilation, vasovagal reactions or panic attacks. These may not fit accurately with a hypersensitivity reaction to CM. In addition, patient's history can include diseases like severe asthma, mastocytosis or the use of medication that may be associated with an increased risk to hypersensitivity reactions.

For the physician administering the CM it is often not clear how to deal with this kind of situations and whether prophylactic medication is indicated. In addition, the literature on the effectiveness of premedication prior to CM administration remains unclear.

All types of contrast media can give hypersensitivity reactions. See further the Introduction to this section.

All types of contrast media will be evaluated: iodine-based, gadolinium-based, microbubble, CM. Also, all types of administration routes will be covered, intravascular (intravenous or intra-arterial), oral and rectal, intracavitary (joints or bladder), and intraductal (bile or pancreatic ducts). See separate chapter for nonvascular CM administration.

Literature search and selection

To answer our clinical question a systematic literature analysis was performed for the following research questions:

1) What factors are related to an increased risk of developing hypersensitivity reactions after contrast administration?

P (patient category): patients undergoing radiological examinations with contrast media;
I (intervention): presence of prognostic factors;
C (comparison): absence of prognostic factors;
O (outcome) allergic reactions to contrast, hypersensitivity reaction, type I / type IV, severe allergic reaction.

2) What are the effects of a prophylactic measure to prevent hypersensitivity reactions after contrast administration compared to a different measure to prevent hypersensitivity reactions after contrast administration or no prophylactic measure, in patients undergoing radiological examinations with contrast media?

P (patients): patients undergoing radiological examinations with contrast media;
I (intervention): prophylactic measure to prevent hypersensitivity reactions after contrast administration;
C (comparison): no prophylactic measure or a different prophylactic measure to prevent hypersensitivity reactions after contrast administration;

O (outcome): allergic reactions to contrast, hypersensitivity reaction, type I/ type IV, severe allergic reaction.

Relevant outcome measures
The working group considered allergic reactions to contrast/ hypersensitivity reactions critical outcome measures for the decision-making process.

Search and select (method)
The databases Medline (OVID), Embase and the Cochrane Library were searched from 1st of December 1980 to 4th of December 2017 using relevant search terms for systematic reviews (SRs), randomized controlled trials (RCTs) and observational studies (OBS). The literature search resulted in 478 hits: 42 SRs, 129 RCTs and 307 OBS.

Studies were selected based on the following criteria:

- adult patients undergoing radiological examinations with contrast media;
- evaluation of effectiveness of prophylactic measures to prevent hypersensitivity reactions after contrast administration;
- or: Evaluation or identification of factors associated with an increased risk of hypersensitivity reactions after contrast administration. These factors could be treatment related, or patient related. Studies were only included when the identified risk factors were corrected for confounders (multivariate models);
- reports predefined outcome measure: hypersensitivity reactions;
- no reports of case series or exploratory findings (n ≥ 10).

Based on title and abstract a total of 123 studies were selected. After examination of full text, a total of 119 studies were excluded and 4 studies were definitely included in the literature summary. Reason for exclusion is reported in the exclusion table.

Three studies were included for the research question regarding the identification of factors related to associated with an increased risk of hypersensitivity reactions after contrast administration. One systematic review (Tramer, 2006) was included for the research question regarding the comparison of the different prophylactic measures to prevent hypersensitivity reactions after contrast administration. The most important study characteristics and results were included in the evidence tables. The evidence tables and assessment of individual study quality are included.

Summary of the literature

1. Factors related to the risk of hypersensitivity reactions after contrast administration.

Description of studies
A total of 3 studies described factors independently related to the risk of hypersensitivity reactions after contrast administration. All studies presented multivariate models, but no internal or external validation of these models, or the results of application of these models in clinical practice.

Chen (2015) described the risk factors associated with adverse reactions (occurring within 1 hour after contrast administration) in 17,513 patients who were administered iopromide (300 or 370 mgI/mL) contrast during coronary angiography or Pecutaneous Coronary Intervention (PCI). All patients (not high-risk patients only) were included in this multicentre (63 centres in China) study.

Jung (2016) described risk factors for developing a hypersensitivity reaction after re-administration of low-osmolality iodinated contrast medium for enhanced computed tomography in 322 patients with a history of hypersensitivity reactions after low-osmolality contrast administration. A total of 219 (68%) of the patients had a mild reaction, while 82 (26%) had a moderate reaction, and 21 (7%) a severe reaction in their history. Premedication was decided on an individual basis by clinicians and could consist of oral and/or intravenous H1-antihistamines, H2-antihistamins and corticosteroids.

Park (2017) described risk factors for developing a hypersensitivity reaction after administration of low-osmolar iodinated contrast medium for enhanced computed tomography in 150 patients with a history of moderate 130 (87%) to severe 20 (13%) hypersensitivity reactions after contrast administration in 328 instances of re-exposure. Patients received antihistamines and/or corticosteroids as pre-medication, the exact premedication was decided on an individual basis.

Results

Chen (2015) reported that acute adverse drug reactions (ADRs) occurred in 66/17,513 (0.38%) patients undergoing iopromide (300 or 370 mgI/mL) administration during coronary angiography or Percutaneous Coronary Intervention (PCI), out of which 2 ADRs (0.01%) were severe. Most ADRs manifested as nausea vomiting (0.22%) and rash (0.09%).

The following factors were associated with risk of ADR:

- age 50 to 69 versus age < 50 (OR: 0.48, 95% CI: 0.27 to 0.85);
- premedication with corticosteroids (OR: 0.41, 95% CI: 0.18 to 0.97);
- contrast dose ≥ 100mL (OR 0.50, 95% CI 0.30 to 0.82);
- pre-procedural hydration (OR: 0.11, 95% CI: 0.04 to 0.33);
- left main coronary disease (OR: 2.27, 95% CI: 1.15 to 4.48);
- previous ADR to contrast (OR: 9.30, 95% CI: 1.10 to78.84).

Allergic constitution, asthma and sex were not independently associated with the risk of developing an adverse reaction.

Jung (2016) described that 47/322 (15%) of the patients experienced a recurrence of an allergic reaction after low-osmolality iodinated contrast medium administration for computed tomography, despite premedication.

The following factors were associated with an increased risk for developing this second acute allergic-like adverse reaction:

- age (OR: 0.97, 95% CI: 0.94 to 0.99);
- previous severe reaction (OR: 8.88, 95% CI: 2.11 to 37.42);
- not using corticosteroid premedication (OR: 0.28, 95% CI: 0.10 to 0.78) - people that used corticosteroid medications had a lower risk to experience an allergic reaction.

The following factors were not independently associated with the risk of acute allergic-like adverse reactions: sex, bronchial asthma, allergic rhinitis, chronic urticaria, food allergy, other drug allergy, H2-antihistamines premedication.

Park (2017) reported that a recurrence of hypersensitivity reactions after contrast exposure occurred in 64/328 (20%) of the instances of re-exposure to low-osmolar iodinated contrast in patients with a history of moderate or severe reactions.

The following factors were associated with an increased risk for developing this second hypersensitivity reaction:

- age (OR: 0.97, 95% CI 0.94 to 0.99);
- diabetes mellitus (OR: 6.49, 95% CI: 2.38 to 17.71);
- chronic urticaria (OR: 7.61, 95% CI: 1.63 to 35.59);
- drug allergy (OR: 3.69, 95% CI: 1.18 to 11.56);
- Changing the iodinated contrast medium (OR: 0.33, 95% CI: 0.17 to 0.64);
- initial hypersensitivity reaction was severe (OR: 2.67, 95% CI: 1.05 to 6.79).

The following factors were not independently associated with the risk of developing a recurrent hypersensitivity reaction: sex, use of premedication.

Level of evidence

For all the included patient populations the quality of certainty of evidence for the prognostic factors was downgraded from high to low by two points, due to risk of bias and indirectness: the prognostic factors were identified, but the prognostics model was not validated internally and externally. The value of the applicability of the multivariate models in a clinical decision-making process was not evaluated.

2. Prophylactic measures to prevent hypersensitivity reactions after contrast administration

Description of studies

One systematic review (Tramer, 2006) that included 9 RCTs was included in this analysis. The goal of this review was to review the efficacy of pharmacological prevention of serious reactions to iodinated contrast media. A systematic search was performed up to October 2005. The pre-specified inclusion criteria were random allocation of patients, use of premedication alone or in combination, presence of a placebo or a no treatment control group, and reporting of presence or absence of allergic reactions. A total of 9 trials with 10,011 adult patients were included in the review analysis. No RCTs that answered the search question were found that were published after Tramer, 2006.

Results

Tramer (2006) reported 9 trials (including 10,011 adults) tested H1 antihistamines, corticosteroids, and an H1 to H2 combination. No trial included exclusively patients with a history of allergic reactions. Many outcomes were not allergy related, and only a few were potentially life threatening. No reports on death, cardiopulmonary resuscitation, irreversible neurological deficit, or prolonged hospital stays were found. In two trials, 3/778 (0.4%) patients who received oral methylprednisolone 2×32 mg or intravenous prednisolone 250 mg had laryngeal oedema compared with 11/769 (1.4%) controls (odds ratio 0.31, 95% confidence interval 0.11 to 0.88). In two trials, 7/3093 (0.2%) patients who received oral methylprednisolone 2×32 mg had a composite outcome (including shock, bronchospasm, and laryngospasm) compared with 20/2178 (0.9%) controls (odds ratio 0.28, 0.13 to 0.60). In one trial, 1/196 (0.5%) patient who received intravenous clemastine 0.03 mg/kg and cimetidine 2 to 5 mg/kg had angio-oedema compared with 8/194 (4.1%) controls (odds ratio 0.20, 0.05 to 0.76).

Table 1 Details of included trials

References	Quality of data reporting (R-C-B-F)*	Premedication and control (No analysed)	Radiological intervention (No analysed)	Excluded patients	Contrast medium
Bertrand et al, 1992[w3]	1-0-2-0	Hydroxyzine 100 mg PO 12 h before (200); placebo PO (200)	IV urography (297); CT scan (93); venography (10)	Allergy, atopy, previous reaction to CM, drug hypersensitivity	Meglumine; ioxaglate
Chevrot et al, 1988[w4]	1-0-0-0	Betamethasone 8 mg IV with CM (109); no treatment (112)	IV urography; CT scan; venography	None	4 ionic IV CM (92%: ionic high osmolar)
Ginsberg et al, 1996[w5]	1-0-1-0	Dexamethasone 4 mg PO 4×/d for 24 h (42); placebo PO (44)	Myelography	None	Iohexol (intrathecal)
Lasser et al, 1987[w1]	1-1-2-0	Methylprednisolone 2×32 mg PO evening and 2 h before (2513, group 1); methylprednisolone 32 mg PO 2 h before (1759, group 2); placebo PO as for group 1 (1603); placebo PO as for group 2 (888)	IV injection	Previous reaction to CM	Any ionic
Lasser et al, 1994[w2]	1-0-2-1	Methylprednisolone 2×32 mg PO 6-24 h and 2 h before (580); placebo PO (575)	Urography; CT scan	None	Iohexol; ioversol
Ring et al, 1985[w6]	1-0-0-1	Prednisolone 250 mg IV (198); clemastine 0.03 mg/kg IV (191); clemastine 0.03 mg/kg + cimetidine 2-5 mg/kg (according to renal function) IV (196); placebo (saline) IV (194); timing not specified	IV urography	Previous reaction to CM	Meglumine; amidotrizoate
Small et al, 1982[w7]	1-0-0-0	Chlorpheniramine 10 mg SC 15 min before (78); placebo (saline) SC (71); no treatment (71)	IV pyelography	None	Not specified
Smith et al, 1995[w8]	1-0-2-1	Dimenhydrinate 25 mg IV 15 to 45 min before (150); placebo (saline) IV (149)	Arteriography	None	Ioxaglate
Wicke et al, 1975[w9]	1-0-1-0	Clemastine 2 mg IV with CM (92); placebo (saline) IV (116)	Urography (148); cholangiography (60)	None	Amidotrizoate; meglumine

CM=contrast medium; CT=computed tomography; IV=intravenously; PO=orally; SC=subcutaneously.
*Randomisation (R): 0=none, 1=mentioned but not specified, 2=mentioned and adequate. Concealment of treatment allocation (C): 0=none; 1=yes. Blinding (B): 0=none, 1=incomplete, 2=patient and caregiver and observer blinded. Follow-up (F): 0=none reported, 1=incomplete, 2=complete (intention to treat analysis possible).

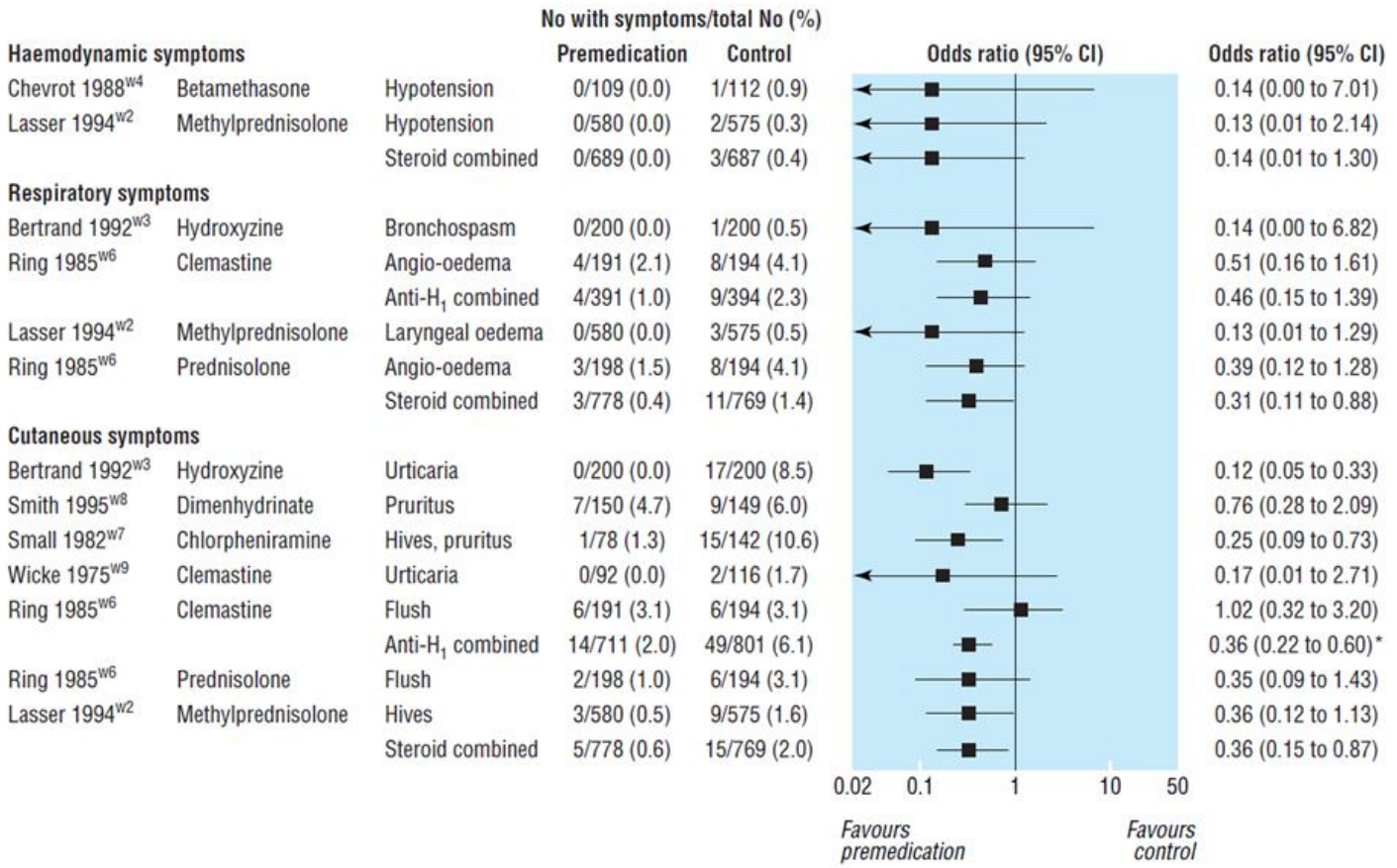

Fig 2 Distinct haemodynamic, respiratory, and cutaneous symptoms. Hypotension, bronchospasm, angio-oedema, and laryngeal oedema were considered to be potentially life threatening. Anti-H=antihistamine. **P* for heterogeneity=0.03, I^2=62%

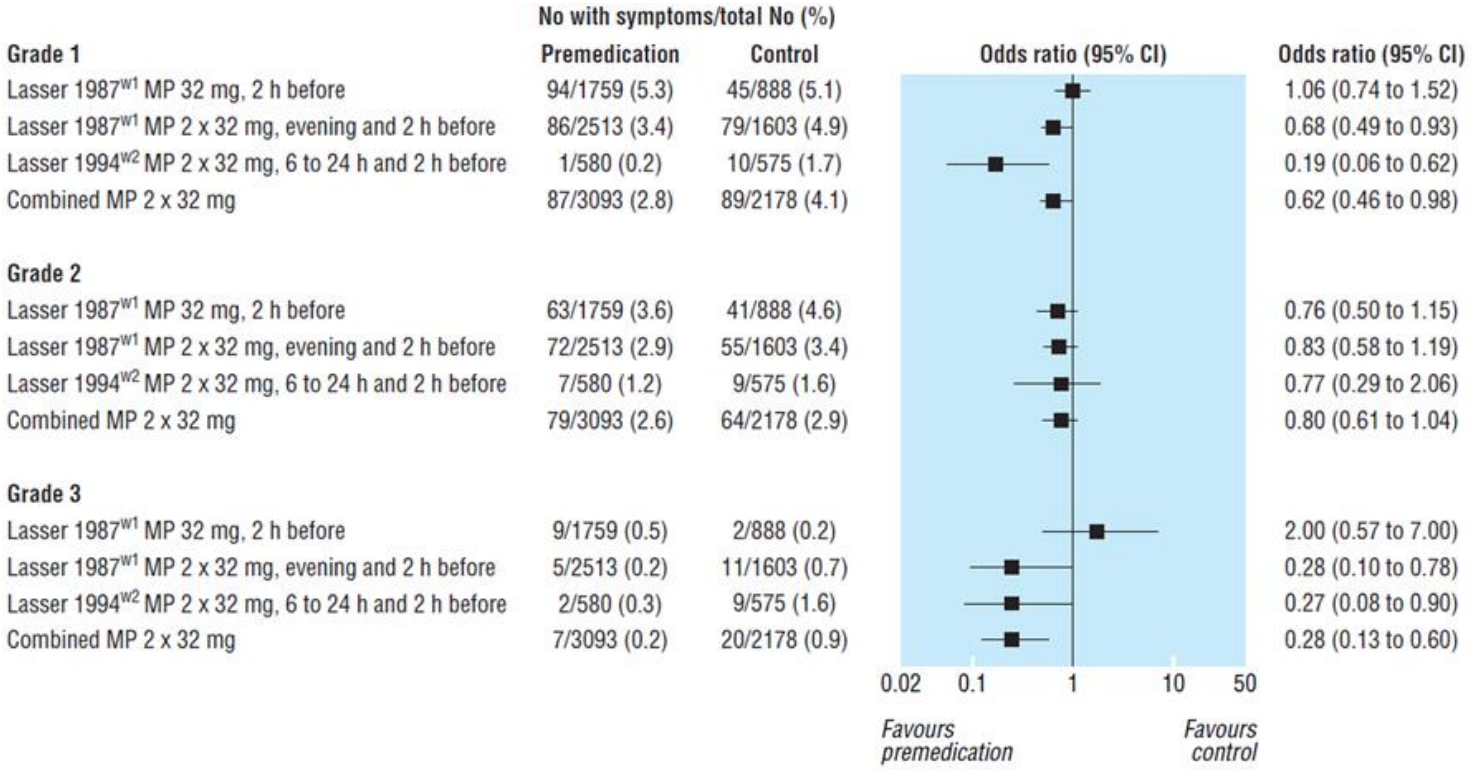

Fig 3 Arbitrary symptom combinations ("grades") as defined in the original reports.[w1 w2] Grade 1=single episode of emesis, nausea, sneezing, or vertigo; grade 2=hives, erythema, emesis more than once, or fever or chills (or both); grade 3=shock, bronchospasm, laryngospasm or laryngeal oedema, loss of consciousness, convulsions, fall or rise in blood pressure, cardiac arrhythmia, angina, angio-oedema, or pulmonary oedema. Grade 3 was considered to be potentially life threatening. MP=methylprednisolone (oral)

Level of evidence

The quality of certainty of evidence for the outcome hypersensitivity reaction was downgraded from high to very low due to risk of bias (as described below), heterogeneity of included studies, inconsistency of results and imprecision of outcome measures (low numbers of events).

The risk of bias of the included studies was deemed high: in no report was an adequate randomisation method described, and only in one was treatment allocation concealed. In four reports, evidence existed of adequate blinding of patients, caregivers, and observers. No report described a complete patient follow-up that enabled an intention to treat analysis.

Conclusions

Factors related to the risk of hypersensitivity reactions after contrast administration.

Low GRADE	The following factors were associated with an increased risk of adverse drug reaction in patients undergoing coronary angiography or percutaneous coronary intervention and receiving iopromide contrast: • age < 50 years; • no premedication with corticosteroids; • contrast dose < 100mL; • no pre-procedural hydration; • left main coronary disease; • previous ADR to contrast. Allergic constitution, asthma and sex were not independently associated with the risk of developing an adverse reaction. *Source: (Chen, 2015)*

Low GRADE	The following factors were associated with an increased risk for developing this second acute allergic-like adverse reaction in patients with a history of a hypersensitivity reaction after low-osmolality contrast administration, who were undergoing another enhanced computed tomography with low-osmolality contrast medium and receiving premedication: • younger age; • previous severe reaction; • no corticosteroid premedication. The following factors were not independently associated with the risk of acute allergic-like adverse reactions: sex, bronchial asthma, allergic rhinitis, chronic urticaria, food allergy, other drug allergy, H2-antihistamines premedication. *Source: (Jung, 2016)*

Low GRADE	The following factors were associated with an increased risk for developing this second hypersensitivity reaction in patients with a history of a moderate or severe hypersensitivity reaction after low-osmolality contrast administration, who were undergoing another enhanced computed tomography with low-osmolality contrast medium and receiving premedication:

	• younger age; • diabetes mellitus; • chronic urticaria; • drug allergy; • not changing the iodinated contrast medium; • Initial hypersensitivity reaction was severe. The following factors were not independently associated with the risk of developing a recurrent hypersensitivity reaction: sex, use of premedication. *Source: (Park, 2017)*

Prophylactic measures to prevent hypersensitivity reactions after contrast administration

Very low GRADE	It is unclear whether the use of premedication decreases the risk of life-threatening anaphylactic reactions. The administration of H1-antihistamines immediately prior to the administration of contrast may decrease the risk of developing hypersensitivity reactions due to iodinated contrast. The administration of corticosteroids given in two doses, 6 hours prior and 2 hours prior to the administration of contrast, both iodinated and non-iodinated, may decrease the risk of developing hypersensitivity reactions due to contrast administration. *Source: (Tramer, 2006)*

Considerations

First and foremost, in patients with a (documented) history of a hypersensitivity reaction to a contrast medium, consider an alternative imaging modality first. In many cases, CT with iodinated contrast media can be replaced by ultrasound, with or without contrast media, or MRI, with or without contrast media. When this is not possible, consider performing the examination without a contrast medium, but only if this has an acceptable degree of diagnostic quality. For this, close communication with the referring specialist is mandatory.

When evaluating hypersensitivity reactions, it is difficult to compare literature. In the literature, adverse effects or adverse reactions are often reported which also include (severe) physiologic effects to contrast medium administration and chemotoxic effects. Anxiety may play a role in hypersensitivity reactions (Lalli, 1974).

Based on the available literature it is not possible to conclusively identify a group of patients that is at increased risk for hypersensitivity and should routinely receive premedication prior to contrast administration. In the ACR Manual on Contrast Media v.10.3 (ACR, 2017) and the ESUR v10 guidelines (Clement, 2014; ESUR 2017), the most significant risk factor for increased risk of hypersensitivity reactions remains a documented history of a previous hypersensitivity reaction to a contrast medium. Patients with atopy/ bronchial asthma or multiple allergies could not be established as a consistent risk factor (Chen, 2015; Jung, 2016).

The evidence regarding the effectivity of corticosteroids and antihistamines for pharmacological prevention is very heterogeneous and of low quality (Tramer, 2006;

Dawson, 2006; Davenport, 2015). It seems that prophylactic premedication can prevent the number of hypersensitivity reactions after contrast administration, but premedication mainly reduces the number of mild reactions and therefore the total number of reactions (Lasser, 1994). There is little data that premedication reduces the number of moderate and severe hypersensitivity reactions, and its use should therefore be limited.

It was believed that premedication with corticosteroids and H1-antihistamines do not have serious side effects and is not costly. However, recently it has been shown that premedication was associated with brief hyperglycaemia (Davenport, 2010), but also with longer hospital stay, increased costs, and worse clinical outcomes (Davenport, 2016).

The old protocols for premedication (Greenberger, 1984; Greenberger, 1986; Lasser, 1994) are still in widespread use (often slightly modified), but there is no literature to establish an optimal indication or protocol. Recently the Greenberger protocol has been challenged by newer, shorter options for inpatients (Mervak, 2017).

Greenberger protocol (elective examinations 1984):
- Prednisolone 50 mg IV - 13h, 7h and 1h before the procedure.
- Diphenhydramine 50 mg IV - 1h before the procedure.

Greenberger protocol (emergency examinations 1986):
- Hydrocortisone 200 mg IV - immediately and every 4h until procedure is finished
- Diphenhydramine 50 mg IV - 1h before the procedure

Lasser protocol (elective examinations 1994):
- Methylprednisolone 32 mg IV - 12h and 2h before the procedure.

In addition, premedication is not perfect. In 2 to 17% of premedicated patients so-called "breakthrough" hypersensitivity reactions can occur despite premedication. These are usually of similar severity as the original culprit reaction for which premedication was prescribed and seldom severe (Davenport, 2009; Mervak, 2015; Lee, 2017).

Another main problem is the registration of contrast media in radiology information systems. For a long time, contrast media have not been treated as drugs. Therefore, in many hospitals iodine-based and other contrast media are "doomed" as a group when a single hypersensitivity reaction to one specific agent occurs, without much testing of the specific culprit agent. Like all drugs, hypersensitivity should nowadays be approached at agent level and not at group level. There is growing evidence that suggests that switching to another agent may be an effective strategy (Abe, 2016; Lee, 2017; Park, 2017).

Premedication of late hypersensitivity reactions
There is a paucity of data on the benefits of premedication for non-severe late hypersensitivity reactions. Most of these reactions are self-limiting or can be treated symptomatically. Major international guidelines suggest to perform allergologic skin testing, but do not recommend the use of premedication for non-severe late reactions (ESUR 2018, ACR 2018).

Recommendations (see also Flowcharts 1 - 4)

I Patients with a previous (acute) hypersensitivity reaction to a known ICM or GBCA

A Elective (plannable) examinations with ICM or GBCA

In all patients with a (documented) history of a hypersensitivity reaction to an iodine-based or gadolinium-based CM, consider an alternative imaging modality. When this is not possible, consider performing an unenhanced exam, but only if this has an acceptable reduction in diagnostic quality.

If the previous hypersensitivity reaction was mild:

- Choose a different ICM or GBCA*.
- Observe the patient ≥ 30 min with IV in place.
- Be vigilant to react to a possible new hypersensitivity reaction.

If the previous hypersensitivity reaction was moderate:

- Choose a different ICM or GBCA*.
- Observe the patient ≥ 30 min with IV in place.
- Be vigilant to react to a possible new hypersensitivity reaction.

In cases of doubtful severity consider referring the patient to a drug allergy specialist for allegologic skin testing with a panel of different iodine-based or gadolinium-based CM.

If the previous hypersensitivity reaction was severe:

- If clinically reasonable, defer the imaging study until the results of allergologic skin testing are available.
- Refer the patient to a drug allergy specialist for allegologic skin testing with a panel of different iodine-based or gadolinium-based CM.
- Apply the advice of the drug allergy specialist for future CM administration.
- Premedicate with2 x 25 mg prednisolone PO/IV** 12h and 2h before CM administration and 2mg clemastine IV within 1h before CM administration.
- Observe the patient ≥ 30 min with IV in place.
- Be vigilant to react to a possible new hypersensitivity reaction.

B Acute (within hours) or emergency (direct) examinations with ICM or GBCA

In all patients with a (documented) history of a hypersensitivity reaction to an iodine-based CM, consider an alternative imaging modality. When this is not possible, consider performing unenhanced exam, if this has an acceptable reduction in diagnostic quality.

If the previous hypersensitivity reaction was mild:

- Choose a different ICM or GBCA*.
- Observe the patient ≥ 30 min with IV in place.
- Be vigilant to react to a possible new hypersensitivity reaction.

If the previous hypersensitivity reaction was moderate:

- Premedicate with 50 mg prednisolone IV** and 2mg clemastine IV within 30min before CM administration.
- Choose a different ICM or GBCA*.
- Observe the patient ≥ 30 min with IV in place.
- Be vigilant to react to a possible new hypersensitivity reaction.

If the previous hypersensitivity reaction was severe:

- Premedicate with 50 mg prednisolone IV** and 2mg clemastine IV within 30min before CM administration.

- Choose a different ICM or GBCA*.
- Observe the patient ≥ 30 min with IV in place.
- Be vigilant to react to a possible new hypersensitivity reaction.

II Patients with a previous (acute) hypersensitivity reaction to an unknown ICM or GBCA

A Elective (plannable) examinations with ICM or GBCA

In all patients with a (documented) history of a hypersensitivity reaction to an iodine-based or gadolinium-based CM, consider an alternative imaging modality. When this is not possible, consider performing an unenhanced exam, but only if this has an acceptable reduction in diagnostic quality.

If the previous hypersensitivity reaction was mild:
- Proceed with the radiologic examination normally.
- Observe the patient ≥ 30 min with IV in place.
- Be vigilant to react to a possible new hypersensitivity reaction.

If the previous hypersensitivity reaction was moderate:
- Proceed with the radiologic examination normally.
- Observe the patient ≥ 30 min with IV in place.
- Be vigilant to react to a possible new hypersensitivity reaction.

In cases of doubtful severity consider referring the patient to a drug allergy specialist for allergologic skin testing with a panel of different iodine-based or gadolinium-based CM.

If the previous hypersensitivity reaction was severe:
- If clinically reasonable, defer the imaging study until results of allergologic skin testing are available.
- Refer the patient to a drug allergy specialist for allergologic skin testing with a panel of different iodine-based or gadolinium-based CM.
- Apply the advice of the drug allergy specialist for future CM administration.
- Premedicate with 2 x 25 mg prednisolone PO/IV** 12h and 2h before CM administration and 2mg clemastine IV within 1h before CM administration.
- Observe the patient ≥ 30 min with IV in place.
- Be vigilant to react to a possible new hypersensitivity reaction.

B Acute (within hours) or emergency (direct) examinations with ICM or GBCA

In all patients with a (documented) history of a hypersensitivity reaction to an iodine-based or gadolinium-based CM, consider an alternative imaging modality. When this is not possible, consider performing unenhanced exam, if this has an acceptable reduction in diagnostic quality.

If the previous hypersensitivity reaction was mild:
- Proceed with the radiologic examination normally.
- Observe the patient ≥ 30 min with IV in place.
- Be vigilant to react to a possible new hypersensitivity reaction.

If the previous hypersensitivity reaction was moderate:
- Premedicate with 50 mg prednisolone IV** and 2mg clemastine IV within 30min before CM administration

- Proceed with the radiologic examination normally.
- Observe the patient ≥ 30 min with IV in place.
- Be vigilant to react to a possible new hypersensitivity reaction.

If the previous hypersensitivity reaction was severe:
- Premedicate with 50 mg prednisolone IV** and 2mg clemastine IV within 30min before CM administration
- Proceed with the radiologic examination normally.
- Observe the patient ≥ 30 min with IV in place.
- Be vigilant to react to a possible new hypersensitivity reaction.

III Patients with a previous breakthrough reaction to CM

In patients with breakthrough hypersensitivity reactions to iodine-based or gadolinium-based CM apply the same as above, but always refer the patient to a drug allergy specialist for allergologic skin testing with a panel of different ICM or GBCA.

IV Patients with previous (acute) hypersensitivity reactions to multiple CM

In patients with hypersensitivity reactions to multiple iodine-based or gadolinium-based CM (either 2 or more different iodine-based CM or gadolinium-based CA or to an iodine-based CM and a gadolinium-based CA) apply the same as above, but always refer the patient to a drug allergy specialist for allergologic skin testing with a panel of different ICM and GBCA

V Patients with previous non-severe late hypersensitivity reactions to CM

In patients with previous mild or moderate late hypersensitivity reactions to iodine-based CM or gadolinium-based CA premedication is not recommended, even in acute or emergency examinations.

Notes

* Consider cross-reactivity of iodine-based CM (see Introduction to this section, table 2).

**Or equivalent dose of another glucocorticosteroid
25 or 50 mg prednisolone is equivalent to:
- 20 or 40 mg methylprednisolone.
- 4 or 8mg dexamethasone.
- 100 or 200mg hydrocortisone.

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Validity and updating

Module[1]	Control holder(s)[2]	Year of authorisation	Next assessment actuality guideline[3]	Frequency of assessing actuality[4]	Who monitors actuality[5]	Relevant factors for changes in recommendations[6]
Prophylaxis of hypersensitivity reactions	NVvR	2019	2024	5 years	NVvR	New tests or new information on diagnostic parameters of tests available

[1] Name of module
[2] Responsible authors (per module)
[3] Year in which the guideline should be assessed for updating
[4] Time frame: Once every 6 months, one year, two years, five years, or longer
[5] Responsible scientific society
[6] Variety of reasons: new drugs, new therapies, et cetera

Module 5a Hypersensitivity Reactions after Nonvascular CM Administration

Introduction

There was few good data to structurally search and critically assess the literature on hypersensitivity reactions after nonvascular contrast media (CM) administration, such as gastro-intestinal administration, urogenital administration, intrabiliairy administration, and intra-articular administration.

Therefore, the guideline committee decided that it was more appropriate to provide an expert-opinion review of the available literature separately and to try to provide recommendations for practice.

Considerations

1. Gastro-intestinal administration

Barium sulphate suspensions are used more and more infrequently in fluoroscopy than in the 1970 and 1990s. Commercial barium sulphate suspensions are inert and not absorbed by the gastrointestinal mucosa. Trace amounts of barium ions may be absorbed by mucosa and stored in soft tissue or bone (Skucas 1997). Hypersensitivity reactions to barium sulphate are exceedingly rare and are usually mild. They have been estimated to occur in about 1 : 1,000,000 cases (Janower, 1986). Yet, severe reactions have been published as case reports in the heyday of barium use, but are exceedingly rare (Seymour, 1997).

It is probable that hypersensitivity reactions are not true reactions to barium sulphate but rather to additives of the commercial barium preparations such as methylparaben or carboxymethylcellulose. In addition, they may also be attributed to the use of glucagon in upper or lower GI studies (Gelfand, 1985).

Iodine-based contrast media (ICM) are widely used in CT to opacify and/or distend the stomach and bowel structures, either via oral intake, via a nasogastric or nasoduodenal tube, or via direct rectal administration. The use of fluoroscopy of the GI system is rapidly declining. The use of (CT) fistulography for entero-cutaneous fistula is also included here.

For high-density (positive) contrast, the older high-osmolar ionic ioxithalamate meglumine and sodium meglumine amidotrizoate are still widely used for this purpose. In CT, water or low-density (negative) CM (Mannitol or PEG) are used more frequently.

In contrast to barium sulphate, small amounts of iodine-based CM are absorbed by the gastro-intestinal mucosa (in the order of 0 to 2%) (Sohn, 2002), with relatively more absorption in the upper than in the lower gastrointestinal system. This absorption may be slow. Therefore, also iodine-based CM can elicit hypersensitivity reactions of all severities, both acute and delayed reactions (Miller, 1997; Schmidt, 1998; Davis, 2015; Böhm, 2017). There is no convincing data that inflammation or ischemia of bowel walls lead to more hypersensitivity reactions.

Angioedema may also occur in the small bowel and is often under diagnosed as it results in atypical abdominal discomfort (Chen, 2012; Hu, 2012). It is probably more frequently caused by intravascular ICM and GBCA administration, and may be mediated via the gut-associated lymphoid tissue (GALT) in the bowel wall (Böhm, 2017).

Because iodine-based CM in CT is usually administered intravenously and orally, the true incidence of gastro-intestinal CM administration is difficult to determine. As published cases are limited to case reports, the incidence is probably very low, much lower than the incidence after intravascular iodine-based CM administration.

Gadolinium-based contrast agents (GBCA) are only rarely used for gastrointestinal use in everyday practice. These GBCA can be absorbed by gastro-intestinal mucosa in small amounts. Given the very low incidence of hypersensitivity reactions to intravascular GBCA, the risk of hypersensitivity reactions is largely theoretical.

2. Urogenital administration

Iodine-based contrast media are used for a variety of fluoroscopic urologic procedures such as cystography, pyelography, nephrostomography, urinary diversions and neobladders, urodynamic examinations, or retrograde urethrography.

As in gastro-intestinal applications, the urothelium can also absorb these CM in small amounts (Davis, 2015), with a potentially higher rate if CM is injected under pressure or if drainage of CM is slow. Therefore, urologic administration can elicit hypersensitivity reactions of variable severity (Weese, 1993; Miller, 1995), even breakthrough reactions (Armstrong, 2005). As shown by one large published series and selected case reports, the incidence of reactions is low (Cartwright, 2008). Nevertheless, in a recent survey with a low response rate by members of the Society of Endourology, hypersensitivity reactions were reported by a considerable number of selected respondents during their careers (Dai ,2018).

In hysterosalpingography the incidence of hypersensitivity reactions following use iodine-based CM is very low, even after venous intravasation (Sanfilippo, 1978; Lindequist, 1991; La Fianza, 2005).

Gadolinium-based contrast agents are virtually never used directly for urogenital procedures and no data on hypersensitivity is available.

3. Biliary system administration

Iodine-based contrast media are mainly used during diagnostic or interventional endoscopic retrograde cholangiopancreatography (ERCP) and in percutaneous transhepatic cholangiography (PTC) with or without drain (PTCD) placements.

There is some systemic absorption of CM after ERCP in the biliary tract, in which the contrast can be detected in the kidneys afterwards. Therefore, also biliary procedures may elicit hypersensitivity reactions to iodine-based CM. However, as shown in the largest published series, the incidence of hypersensitivity reactions during ERCP is very low, even in high-risk patients (Dragonov, 2008; Trottier-Tellier, 2018).

Gadolinium-based contrast agents are virtually never used directly for biliary procedures and no data on hypersensitivity is available.

4. Intra-articular administration

Iodine-based contrast media are frequently used for arthrography, single/double-contrast CT arthrography or to help guide needle placement in MR Arthrography.

The intra-articular contrast can be absorbed in small amounts by the synovium. Hypersensitivity reactions have been described with severe reactions occurring in incidental

patients (Newberg, 1985; Westesson, 1990; Hugo III, 1998). However, in two large surveys of 126,000 and 262,000 arthrograms the risk of hypersensitivity reactions was low, and most reactions were mild (Newberg, 1985; Hugo III, 1998).

Gadolinium-based contrast agents are used for MR arthography in a very diluted amount (2 mmol/L or a 1:250 dilution).

Similar to iodine-based CM, trace amounts of GBCA can be absorbed by synovium. However due to the dilution the number of hypersensitivity reactions following MR arthrography is almost non-existent (Schulte-Altedorneburg, 2003).

5. Miscellaneous

Iodine-based contrast media are or have been used for a number of miscellaneous procedures like (CT) discography, sialography, et cetera.

Hypersensitivity reactions in most of these procedures are not documented well enough to discuss them in this guideline, or have fallen in disfavour.

Recommendations

Small amounts of ICM or GBCA can be absorbed by mucosa and enter the systemic circulation after all types of nonvascular CM administration.

Hypersensitivity reactions after nonvascular administration of ICM and GBCA can occur, but their incidence is low to very low.

No preventive measures are indicated for ERCP or for nonvascular GBCA administration.

For other indications using ICM no firm recommendations can be given for patients that have experienced hypersensitivity reactions to CM in the past.

In patients that have experienced *severe* hypersensitivity reactions to CM in the past, alternative imaging or contrast agents should be explored with the radiologist, and a strict indication for examinations using nonvascular CM administration is needed.

In patients that have experienced *severe* hypersensitivity reactions to CM in the past, preventive measures for severe reactions as outlined in Module 5 may be followed prior to examinations using nonvascular CM administration, if possible after laboratory and skin testing by a specialist in drug allergy prior to the examination.

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Introduction to Safe Use of Gadolinium-Based Contrast Agents

Gadolinium-based contrast agents (GBCAs) are routinely used in patients undergoing magnetic resonance imaging (MRI) to enhance image contrast and thereby improving detection and characterization of lesions. These agents exploit the highly paramagnetic nature of gadolinium (Gd), which alters the local magnetic properties shortening both T_1 and T_2 of tissue leading to increased signal intensity on T_1-weighted images (and reduced signal intensity on T_2-weighted images) (Elster). Since their introduction in 1988, GBCAs have been administered worldwide, with an estimate of 550 million doses being delivered (Balzer, 2017; McDonald, 2018; Endrikat, 2018). At present, roughly 30 to 45% of the MRI scans use GBCAs, with an estimated use of 40 million doses per year (Endrikat personal communication).

I Gadolinium Physicochemistry

Gadolinium and relaxivity

Gadolinium (Gd; Z = 64 and MW = 157,25 g/mol) is a rare earth metal from the Lanthanide family of elements in the periodic system. It has seven unpaired electrons in its 4f orbitals, has a high magnetic moment, and a very long electron spin relaxation time (Caravan, 1999; Lin, 2007; Hao, 2012).

The efficiency of T1-weighted contrast agents in aqueous solutions is determined by its relaxivity ($r_1 = 1 / T_1$). The relaxivity is determined by relaxation effects of water molecules interacting directly with the paramagnetic ion (inner sphere) and interactions with closely diffusing water molecules without interacting with the M-L complex (outer sphere).

For clinical GBCA 60% of relaxivity comes from inner sphere effects and 40% from outer sphere effects. Chelated gadolinium complexes are monohydrated ($Gd(H_2O)^{3+}$), as in their spherical configuration there is only enough space around the gadolinium for one (inner sphere) water molecule that exchanges rapidly with other nearby water molecules (outer sphere) (De Leon-Rodriguez, 2015).

Gadolinium chelation and stability constants

In biological systems, unchelated Gd^{3+} ions are toxic because the ion has an ionic radius (107,8 pm) close to the ionic radius of Ca^{2+} (114 pm) and can bind to Ca^{2+} ion channels and Ca^{2+}-dependent proteins such as metalloenzymes or messenger proteins like calmodulin or calexitin.

To suppress this potential toxicity, the Gd^{3+} ions must be tightly bound to an organic ligand to form a metal-ligand (ML) complex or chelate. The ligand will reduce toxicity, change the tissue distribution, and influence relaxivity. In the current European situation, such ligands are macrocyclic (DOTA, BT-DO3A or HP-DO3A) or linear (BOPTA or EOB-DTPA) (Table 1).

Normally, equilibrium exists for the reaction between metal M and ligand L.
The reaction can be written as: $(M) + (L) \leftrightarrow (ML)$

The stability of the Gadolinium-ligand complex can be described by a number of constants.

The logarithm of the thermodynamic stability constant K_{therm} describes the affinity of Gd for the ligand, and is normally measured at pH = 14. Higher values imply a higher stability.
$K_{therm} = (ML) / (M) \cdot (L)$.

For biological systems more appropriate is the logarithm of the apparent or conditional thermodynamic stability constant K_{cond}, which considers the total concentration of the free ligand, including all its protonation states. It characterizes the affinity of Gadolinium for ligand in aqueous media under physiologic conditions (pH = 7,4). In all GBCA the conditional stability is substantially lower than the thermodynamic stability. K_{cond} = (ML) / (M) · {(L) + (HL) + (H_2L) + …….}

The kinetic stability describes the kinetic rate of the dissociation of the Gadolinium-Ligand complex. It is closely related to the thermodynamic stability and is most commonly described as the half-life of the dissociation of the Gd-Ligand complex or by the observed dissociation constant k_{obs}. To be measurable, such kinetic analyses are done under acidic conditions at pH =1 (Port, 2008). Dissociation rate = k_{obs} (ML).

Some commercial solutions of contrast media contain variable amounts of free ligands or calcium complexes to ensure chelation of any free Gd^{3+} or other metal traces from the vial during its shelf life. This amount is often used as indirect indicator of the instability of the compound.

The thermodynamic stability constants are a measure of how much uncomplexed Gd^{3+} will be released in biologic tissues if the system reaches equilibrium. In vivo, such new thermodynamic equilibrium is usually not reached as most of the complex is excreted long before any uncomplexed gadolinium can be released. Therefore, the kinetic stability is in vivo much more important than the thermodynamic stability.

Transmetallation

Transmetallation is the exchange between Gd^{3+} and other metal ions M^{+} that have greater affinity for the chelate. The amount of transmetallation depends on the stability of the chelating ligand. Gadolinium ions can be removed from the Gd-ligand complex by several endogenous positively charged ions like Zn^{2+}, Cu^{2+}, and Ca^{2+} whereby Gd^{3+} is released, while endogenous negatively charged ions like PO_4^{3-} and CO_3^{2-} can compete with the free ligand to form insoluble toxic Gd^{3+} compounds like $GdPO_4$ or $Gd_2(CO_3)_3$ (Idee, 2006).

Transmetallation can be described by the reaction: (Gd-L) + (M^{+}) ↔ Gd^{3+} + (ML)

Of the most frequently described stability constants, a high kinetic stability is regarded as the most important to minimize transmetallation. Since the stability of the macrocyclic Gd chelates is much more limited by the slow release of Gd^{3+} from the complex, the kinetic stability is more important in such ligands.

The main physicochemistry and stability data of current GBCA are summarized in *Table 1*.

Biodistribution and Elimination

After intravenous administration the GBCA is excreted by the kidneys with an early elimination half-life of about 1.5 h in patients with normal renal function. More than 90% of the injected GBCA is cleared from the body within 12 h. This early excretion phase is similar for linear and macrocyclic GBCA.

In patients with severely reduced renal function (eGFR < 30 ml/min/1.73m^2) this elimination half-life for GBCA can increase up to 18-34 h (Joffe, 2008). During that time there is a potential for transmetallation with an increased release of free Gd^{3+} ions (Aime, 2009).

Recent systematic review of pharmacokinetic analysis revealed a deep compartment of distribution with long-lasting residual excretion. This long-lasting excretion is faster for macrocyclic compared to linear GBCA, correlated to the higher thermodynamic stability and differences in transmetallation. In addition, bone residence time for macrocyclic GBCA (up to 30 days) was much shorter than for linear GBCA (up to 2,5 years) (Lancelot, 2016).

II Nephrogenic Systemic Fibrosis (NSF)

Nephrogenic Fibrosing Dermopathy and Nephrogenic Systemic Fibrosis

In 2000, a previously unknown fibrosing skin disorder, resembling scleromyxedema, was first described in haemodialysis patients. At the time it was termed Nephrogenic Fibrosing Dermopathy (NFD) (Cowper, 2000), and the histopathology and differentiating features from other fibrosing disease were described later (Cowper, 2001). Ongoing research revealed that the fibrosis was not limited to the skin and subcutis, but that it was a generalized fibrotic process, which can also involve heart and pericardium, lung and pleura, muscles, diaphragm, renal tubules and the rete testis. Therefore the name was changed to Nephrogenic Systemic Fibrosis (NSF).

In 2006 the use of gadolinium was first linked to the development of NSF in patients with end-stage renal disease who developed NSF within 2-4 weeks after gadodiamide-enhanced MRA (Grobner, 2006). Almost simultaneously, another Danish group reported on thirteen patients (eight dialysis-dependent) who developed NSF after administration of 18,5 ± 5,5 mmol gadodiamide (Marckmann, 2006). The exact aetiology of NSF is unknown. There is a constant association with severe renal insufficiency, usually CKD grade 5 or dialysis. No association with the cause of the renal insufficiency has been shown and there is no indication that dialysis can induce the disease, but many patients have a history of a failed renal transplantation.

Clinical features of NSF

NSF is an illness of all age groups (8 to 87 years) without predilection for race or sex. There can be a fulminant course in 5% of cases. All affected patients have severe chronic kidney disease (CKD), while the majority is dialysis-dependent, either haemodialysis or peritoneal dialysis. The primary cutaneous lesions consist of pink, erythematous papules that coalesce into erythematous plaques and ill-demarcated brawny plaques with a ‘peau d’orange’ surface. The skin (and subcutis) is thickened and has a hardened, woody texture. The extremities are involved most frequently, the legs more often than the arms. Involvement is usually symmetrical, with extension from the ankles to the thighs and from the wrists to the upper arms. The trunk is less frequently involved. Contractures can occur in involved joints, and may lead to severe disability (days to weeks). In the involved extremities itching and sharp pains can be present.

The disease resembles the very rare scleromyxedema. ß2-microglobulin amyloidosis can also induce fibrosis in patients with advanced CKD. Other possible differential diagnoses include scleroderma, morphea (localized scleroderma), scleroedema, eosinophilic fasciitis, calciphylaxis, porphyria cutanea, and even dermatofibrosarcoma protuberans (DFSP). In an early phase there may be overlap with cellulitis, panniculitis, or drug-reactions.

NSF is a clinical and histopathological diagnosis. Laboratory tests are non-specific or related to the underlying disease. A deep skin biopsy shows irregularly thickened collagen- and elastin bundles with clefts and increased deposition of dermal mucin. Between these bundles fibroblastic cells are deposited are positive for CD-34, CD-45RO, and procollagen I. Also, large dendritic cells are present, positive for CD-68 and Factor XIIIa. Leukocytes or

lymphocytes are only present in a limited number. Diagnosis of NSF is currently based on the clinicopathologic Girardi criteria (Girardi, 2011).

There is no effective treatment for NSF, and prevention is therefore very important. Restoring renal function rapidly by renal transplantation may be the best treatment.

End of 2013, the FDA Adverse Event Reporting System included 1603 NSF cases. Cases were associated with GBCA exposure before 2010, while few (if any) cases were associated with GBCA exposure after 2010. Most cases originated from USA in patients aged 51 to 60 years. Of the cases, 88% occurred in stage 5 CKD (eGFR < 15 ml/min/1.73m^2) and 10% in patients with acute renal failure. Among the risk factors, chronic liver disease is no longer a significant risk factor (Smorodinsky, 2015; Fraum, 2017).

Association of NSF with gadolinium-based contrast agents

Many retrospective case-control studies have found a significant association between GBCA administration and the risk of NSF (Edwards, 2014; Zhang, 2017; Zou, 2011). Almost all unconfounded cases (i.e. definitely associated with one GBCA) are associated with linear GBCA, especially gadodiamide, but not with macrocylic GBCA. Risk factor analyses have shown that a higher cumulative linear GBCA dose (either from using high dose injections or a greater number of MRI examinations) and previous inflammatory conditions (either thrombosis or endothelial damage from vascular or transplantation surgery) are associated with increased risk (Van der Molen, 2008; Thomsen, 2016). The initial retrospective studies investigating the association between NSF and GBCA were limited by selection bias. Another important limitation is the considerable geographic differences exist in the number of reported cases, that cannot be explained by differences in patient populations and are thus possibly exist due to differences in reporting of NSF cases or medicolegal systems (Thomsen, 2016; Endrikat, 2018). Of all countries using gadolinium based contrast agents world-wide, one of the countries with the highest NSF awareness, Denmark, reported the highest prevalence worldwide with 12 cases per million inhabitants based on cases reported between 2006 and 2012 (Elmholdt, 2013).

In the published NSF cases that described a link to linear GBCAs, patients presented with symptoms starting within 2-3 months of CM administration. However also much longer delays have been described of even up to 1 to 6 years in limited number of cases. Suggested explanations for this variability between time to linear GBCA exposure and the onset of NSF symptoms are slow mobilization of Gd over time from skin or bone stores.

Analysis of cases registered at Bayer Healthcare revealed that year of market introduction and US market share 2000 to 2007 influenced the absolute number of NSF reports for each GBCA, as well as their a priori probability to cause NSF (Endrikat, 2018).

In the most recent review of 693 patients with biopsy-confirmed NSF, it was shown that only 7 cases were associated with GBCA-exposure after 2008. This indicates that the regulatory actions and practice changes have been very effective. Factors that were associated with NSF included exposure to high-risk GBCA, haemodialysis, pro-inflammatory conditions, β-blockers, hyperphosphataemia, and epoetin. For low-risk GBCA there is no need for screening of renal function prior to contrast administration (Attari, 2019).

III Gadolinium Deposition in the Brain and Body

A. Gadolinium Deposition in the Brain

Clinical studies

In 2014, it was suggested that the retrospectively observed hyperintensity of the dentate nucleus and the globus pallidus relative to the pons (dentate nucleus to pons (DNP) ratio) on unenhanced T_1-weighted images of a population of patients with brain tumours, was related to repeated administrations of linear GBCAs (Kanda, 2014). Almost simultaneously, another group reported similar findings on unenhanced T_1-weighted brain images after multiple injections of gadodiamide in patients with multiple sclerosis and patients with brain metastases (Errante, 2014).

After these initial reports, a multitude of retrospective studies have found increased SI in the dentate nucleus and or globus pallidus for linear GBCA. No such increases were found for macrocyclic GBCA, even after large doses (Radbruch, 2015; Ramalho, 2016; Radbruch, 2017). In a recent systematic review of these studies by the ESMRMB Gadolinium Research Evaluation Committee (now ESMRMB-GREC) it was shown that there was large variety in sequence type and evaluation methodologies (Quattrocchi, 2019).

One of the biggest problems is that increased SI ratios at unenhanced T_1-weighted MRI are a poor biomarker for gadolinium deposition, as SI ratios do not have linear relationship with Gd concentration, and are highly dependent on the MRI parameters used during acquisition. Absolute signal intensity (expressed in arbitrary units) in MRI depends on many MRI parameters such as field strength, sequence type/parameters, coil sensitivity/filling factor, coil tuning/matching drift, etc.. Since little is known about which forms of gadolinium are present (speciation), signal intensities, or changes thereof, will not reflect true changes in gadolinium content (McDonald, 2018; Quattrocchi, 2019).

Preclinical studies
Preclinical studies in rat brains have highlighted the importance of in vivo dechelation of Gd^{3+} ions from less stable GBCAs, regardless of the presence of a renal dysfunction and with a clear dose-effect relationship. All quantities were in the nmol per gram tissue range. They have also shown that differences exist in the amount of total gadolinium retained in the brain when comparing different GBCA compounds (Robert, 2015; Jost, 2016; Robert, 2017; Smith, 2017).

To date it is unclear what forms are responsible for the increased T_1w signal increase (gadolinium speciation). Recently, it was shown that for gadolinium in the rat brain 3 different chemical forms have to be distinguished: intact chelate, gadolinium bound to macromolecules, and insoluble gadolinium salts (Frenzel, 2017). The intact chelates were found for both linear and macrocyclic GBCA, but the other forms only for linear GBCA. As precipitated gadolinium does not induce any MRI signal when excitated, it is likely that the gadolinium bound to macromolecules is responsible for the visible T_1w hyperintensity in clinical MRI (Gianolio, 2017).

Well-conducted long-term animal studies demonstrated that for linear GBCA a large portion of gadolinium was retained in the brain, with binding of soluble gadolinium to macromolecules. For macrocyclic GBCA only traces of the intact chelated gadolinium were present with complete washout in time (Robert, 2018; Jost, 2019).

Intact GBCA does not cross the intact blood-brain barrier. It is now believed that GBCA can reach the CSF via the choroid plexus and ciliary body and can reach the brain interstitium via the glympathic system along perineural sheaths and perivascular spaces of penetrating cortical arteries. GBCA distributed into the cerebrospinal fluid cavity via the glymphatic system may remain in the eye or brain tissue for a longer duration compared to the GBCA in

systemic circulation. The glympathic system may be responsible for deposition in linear GBCA as well as for GBCA clearance (Taoka, 2018; Deike-Hofmann, 2019).

B. Gadolinium Deposition in the Body

Most data mentioned below are all from preclinical studies in animals.

Gadolinium deposition in bone

Lanthanide metals (gadolinium, samarium, europium, and cerium) have long been known to deposit in bone tissue and have effects on osteoblasts and osteoclasts, but the exact mechanisms are not yet well understood (Vidaud, 2012).

Gadolinium deposits have been found in samples of bone tissues of humans at higher concentrations than in brain tissue after administration of linear and macrocyclic GBCA, whereby linear GBCA deposit 4 to 25 times more than macrocyclic GBCA (White, 2006; Darrah, 2009; Wang, 2015; Murata, 2016).

The bone residence time for macrocyclic GBCA (up to 30 days) is much shorter than for linear GBCA (up to 8 years) (Darrah, 2009; Lancelot, 2016). Bone may serve as a storage compartment from which Gd is later released in the body (Thakral, 2007). It is postulated that the long-term reservoir of gadolinium in bones might implicate that some patients with high bone turnover, such as menopausal women and patients with osteoporosis may be more vulnerable to gadolinium deposition (Darrah, 2009).

Gadolinium deposition in skin

Gadolinium depositions in skin have been demonstrated ever since the association of GBCA with nephrogenic systemic fibrosis in 2006. See also section on NSF.

In skin biopsies of NSF patients, gadolinium was found along collagen bundles but also as insoluble apatite-like deposits, suggesting dechelation (Sieber, 2009; Thakral, 2009). After linear GBCA, gadolinium deposits were found up to 40-180 times more frequently than after macrocyclic GBCA, histologic changes are more extensive, and also products of dechelation of GBCA can be found (Haylor, 2012; Wang, 2015).

Recently, gadolinium has also been found in the skin of patients with normal renal function after high cumulative GBCA doses (Roberts, 2016). With normal renal function even a case of ‘gadolinium-associated plaques’ has been described, which suggest that gadolinium deposition in the skin after linear GBCA might give clinically relevant symptoms (Gathings, 2015).

Gadolinium deposition in other organs

Thus far, very little is published about the effects of gadolinium deposition in other organs.

In a clinical study in the liver, gadolinium deposits have been associated with iron overload in the livers of paediatric stem cell transplantation patients with normal renal function, reacting well to iron dechelation therapy (Maximova, 2016).

Based on animal studies, it has been suggested that residual Gd is also present in tissues samples of kidney, liver, spleen, and testis (Tweedle, 1995; Wang, 2015; McDonald, 2017; Di Gregorio, 2018; Mercantepe, 2018; Celiker, 2018; Celiker, 2019). While deposition in the brain was only 2 to 7 µg Gd, the amounts in other organs varied 168 to 2134 µg Gd for

kidney, 16 to 388 µg Gd for liver, and 18 to 354 µg Gd for spleen, all per gram of tissue. In all tissues the level was highest for the linear GBCA gadodiamide (McDonald, 2017).

Self-reported clinical symptoms
Thus far, gadolinium deposition has not been associated with clinical symptoms.
Small online gadolinium toxicity support groups in USA have claimed that their members have manifested symptoms analogous to NSF and have prolonged excretion of Gd in urine following administration of GBCA. Surveys have shown variable symptoms that occur either directly or within 6 weeks of GBCA administration. Most reported symptoms are burning sensation and bone pain in lower arms and limbs, central torso pain, headache with vision/hearing changes, and skin thickening and discoloration (Burke, 2016; Semelka, 2016).

This complex of symptoms was coined "gadolinium deposition disease (GDD)". The critical findings are the presence of gadolinium in the body beyond 30 days, combined with at least 3 of the following features, with onset after the administration of GBCA: i) central torso pain, ii) headache and clouded mentation, iii) peripheral leg and arm pain, iv) peripheral leg and arm thickening and discoloration, and v) bone pain (Semelka, 2016).

Significant differences in gadolinium levels in bone and urine have been observed between individuals experiencing symptoms and those who are not (Lord, 2018). A large study with a control population found more new symptoms within 24 h after exposure to GBCA than after unenhanced MRI. From the GDD-like symptoms, only fatigue and mental confusion were more frequently reported after enhanced MRI, questioning the term GDD (Parillo, 2019).

IV The effect of NSF and the EMA ruling

In many European countries, the described association between NSF and exposure to linear GBCAs in 2006 has resulted in the fact that most hospitals switched early (2007 and onwards) to macrocyclic GBCA use only, in most cases gadoterate or gadobutrol. After the series of publications describing increased signal intensities in the brain nuclei on unenhanced T1-weighted imaging after multiple linear GBCA exposures and post-mortem studies revealing the presence of small amounts of gadolinium in neural tissues, the European Medicines Agency instituted an article 31 procedure which eventually led to the withdrawal of EU market authorizations of the high-risk linear GBCA gadodiamide and gadoversetamide, as well as restrictions on the use of gadopentetate (MR Arthrography only) and, gadobenate (liver imaging only) (EMA, 2017; Dekkers, 2018). Therefore, for general use in MRI only macrocyclic GBCA are available, while the linear GBCA gadoxetate and gadobenate are available for liver-specific MRI.

Gadolinium metabolism and deposition still has many knowledge gaps for which an international research agenda is important. The ACR/NIH/RSNA Meeting 2018 has made a good inventory where future research should be aimed at (McDonald, 2018).

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Table 1 Physicochemical characteristics and stability constants of gadolinium-based contrast agents

Name	Ligand	Structure	Ionicity	Molecular Weight *(Dalton)*	Osmolality *(mOsm/kg)*	Viscosity 37ºC *(mPa s)*	T1 relaxivity in blood, 1.5T[a] *(L/mmol s)*	T2 relaxivity in blood, 1.5T[a] *(L/mmol s)*	Renal Excretion *(T½; hours)*
gadopentetate	DTPA	Linear	Ionic	939.0	1960	2.9	4.3	4.4	1.6
gadodiamide	DTPA-BMA	Linear	Nonionic	537.6	789	1.4	4.6	6.9	1.3
gadobenate	BOPTA	Linear	Ionic	1058.2	1970	5.4	6.7	8.9	1.2-2
gadoxetate	EOB-DTPA	Linear	Ionic	682.0	688	1.2	7.3	9.1	1.0
gadoteridol	HP-DO3A	Macrocyclic	Nonionic	558.7	630	1.3	4.4	5.5	1.6
gadobutrol	BT-DO3A	Macrocyclic	Nonionic	604.7	1390	4.9	5.3	5.4	1.5
gadoterate	DOTA	Macrocyclic	Ionic	558.6	1350	2.0	4.2	6.7	1.6

Name	Ligand	Thermodynamic Stability *(pH 14)* *(Log K_{therm})*	Conditional Stability *(pH 7.4)* *(Log K_{cond})*	Kinetic Stability *(37°C, pH 1)* *(T½; hours)*	Dissociation Constant *Kobs* *(s^{-1})*	Excess Ligand *(mmol/l)*	Stability Classification EMA	Decision EMA 2017
gadopentetate	DTPA	22.5	18.4	0.16	0.58	1	Low	Artho only
gadodiamide	DTPA-BMA	16.9	14.9	0.01	12.7	25	Low	Withdraw
gadobenate	BOPTA	22.6	18.4	NA	0.41	0	Intermediate	Liver only
gadoxetate	EOB-DTPA	23.5	18.7	NA	0.16		Intermediate	Liver only
gadoteridol	HP-DO3A	23.8	17.1	1.6	0.00026	0.5	High	Maintain
gadobutrol	BT-DO3A	21.8	14.7	7.0	0.000028	1	High	Maintain
gadoterate	DOTA	25.6	19.3	23.0	0.000008	0	High	Maintain

NA = not available

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Module 6 Nephrotoxicity of Gadolinium-Based Contrast Agents

Clinical question

How can PC-AKI be prevented after administration of Gadolinium-Based (Gd) Contrast Agents (GBCA)?
Subquestions:

1. Is administration of Gadolinium-Based (Gd) Contrast Agents (GBCA) associated with an increased risk of post contrast acute kidney injury (PC-AKI) compared to placebo/unenhanced imaging?
2. Is there a difference in the risk of PC-AKI between high and low dosage of GBCA?
3. Is there a difference in the risk of PC-AKI between different GBCA?

Introduction

From laboratory testing on cell lines and animals, it is known that Gd chelates are nephrotoxic. In daily practice, this nephrotoxicity is not an issue, as the required dose of these chelates is usually too low to lead to nephrotoxicity in patients.

Search and select criteria

To answer our clinical question a systematic literature analysis was performed.

P (Patient):	patients who received Gadolinium-Based Contrast Agents (GBCA);
I (Intervention):	gadolinium based contrast agents, gadoterate meglumine, gadodiamide, gadobenate dimeglumine, gadopentetate dimeglumine, gadoteridol, gadoversetamide, gadobutrol;
C (Comparison):	no GBCA or another type of GBCA, gadoterate meglumine, gadodiamide, gadobenate dimeglumine, gadopentetate dimeglumine, gadoteridol, gadoversetamide, gadobutrol;
O (Outcomes):	nephrotoxicity (acute and permanent), dialysis, mortality.

Relevance of outcome measures

The working group considered the outcomes nephrotoxicity, mortality and dialysis critical measures and outcome for the decision-making process.

The working group did not define the criteria for the outcomes a priori, but used the outcomes as defined in the studies. The working group considered a clinically relevant difference according to the standards of GRADE: a difference in relative risk of 25% for dichotomous outcomes and a difference of 10% for continuous outcomes (GRADE handbook, web-link in references).

Methods

The databases Medline (OVID), Embase and the Cochrane Library were searched from 1st of January 1996 to March 2018 using relevant search terms for systematic reviews (SRs), randomized controlled trials (RCTs) and observational studies (OBS). The literature search produced 245 hits: 22 SR, 51 RCTs and 172 OBS. Based on title and abstract a total of 15 studies were selected. After examination of full text 7 articles were selected: 4 for subquestion 1, 2 for subquestion 2 and 1 for subquestion 3. Reasons for exclusion are reported in exclusion table (under the Tab “exclusion table”). The most relevant study characteristics of the included studies can be found in the evidence tables.

1. Gadolinium- Based Contrast Agents versus placebo/unenhanced imaging

Summary of the literature

Macrocyclic GBCA

Deray (2013) describe a prospective multicentre non-randomized study, comparing the renal safety of Gd-DOTA (macrocyclic GBCA) enhanced MRI with non-enhanced MRI in 114 patients with eGFR 15 - 60 ml/min/1.73 m^2(Deray, 2013).Gd-DOTA was injected intravenously by a power injector at a dose of 0.1 mmol/kg. PC-AKI was defined as an increase in SC of at least 25% or 44.2mmol/kg above the baseline value. Serum creatinine levels were measured 72±24 hours after the MRI.

Linear GBCA

In a randomized controlled trial by Townsend (2000) 32 patients were included. They were divided into 2 categories, eGFR 30-60 (group 1) and eGFR 10 to 29 ml/min/1.73m^2 (group 2) (Townsend, 2000). Patients in both groups were randomized to be infused with either Gd-BOPTA (linear GBCA) or saline, both at a dose of 0.2 mmol/kg. Both groups maintained saline infusion after the initial bolus and received a total of 250-300 ml saline. No MRI took place after the injection. PC-AKI was defined as an increase in serum creatinine (SC) > 44,2 µmol/l above the baseline value. SC was measured before the injection and for 7 consecutive days after the injection. In group 1, 9 patients received Gd and 6 saline, in group 2, 11 patients received Gd and 6 saline.

Gok Oguz (2013) describes 144 patients with 1 or more risk factors for AKI (advanced age (> 75 years), diabetes mellitus, chronic kidney disease, congestive heart failure, using other nephrotoxins, and hypotension) in a prospective case-control study (Gok Oguz, 2013). Patients were divided into 2 groups, but the article does not state clearly what the criteria are to be included in either one of the groups. All 72 patients (mean eGFR 36 ml/min/1.73m^2) in group 1 received intravenous injection with Gd-DTPA (linear GBCA), whereas all 72 patients (mean eGFR 39 ml/min/1.73m^2) in group 2 received no Gd contrast. PC-AKI was defined as an increase of SC of at least 26.4 µmol/l or ≥ 50% from baseline. Before the MRI and at 6 h, 24 h, 72 h, and 168 h after the MRI, SC was measured.

Trivedi (2009) describe a retrospective study that included 162 patients who underwent MRI with gadodiamide (linear GBCA) and 125 controls that underwent unenhanced MRI (Trivedi, 2009). Patients were included when SC measurements were available during 7 days preceding MRI and 48 to 72 hours after MRI. Baseline eGFR was 103.1 +/- 49.5 ml/min/1.73m^2 in the group receiving Gd and 103.4 +/- 48.4 ml/min/1.73m^2 in the control group. PC-AKI was defined as SC >44.2 micromol/l compared to baseline.

Results

Outcome Post-Contrast Acute Kidney Injury (PC-AKI)

Four studies (Townsend, 2000, Deray, 2013, Gok Oguz, 2013 and Trivedi, 2009) reported on the incidence of PC-AKI after administration of GBCA. Due to the heterogeneity in study designs the results were not pooled.

Macrocyclic GBCA

Deray (2013) reported PC-AKI in one patient after injection with macrocyclic Gd-DOTA (1.4%).

Linear GBCA

There were no cases of PC-AKI in the studies Gok Oguz (2013), Townsend (2000) and Trivedi (2015) using a variety of linear GBCA.

Quality of evidence
The quality of certainty of evidence was graded as very low due to high risk of bias (see Table Risk of Bias assessment, downgraded by one point) and low number of patients (imprecision downgraded by two points).

Outcome Dialysis
Two studies reported on the requirement of dialysis after administration of GBCA. Both studies (Townsend, 2003 (linear GBCA) and Deray, 2013 (Macrocyclic GBCA)) reported that no subjects required dialysis.

Quality of evidence
The quality of certainty of evidence was graded as very low due to the low number of patients (imprecision downgraded by two points).

No studies reported on the outcome mortality.

2. High versus low dose of Gadolinium-Based Contrast Agents

Summary of the literature

Macrocyclic GBCA

Kroencke (2001) randomized 94 patients with suspected abnormality of the abdominal aorta or renal arteries to MR angiography after the IV injection of one of four doses of gadobenate dimeglumine (0.025, 0.05, 0.1, and 0.2 mmol/kg of body weight), a macrocyclic GBCA (Kroencke, 2001). SC was obtained pre-dose and at the 24-hr follow-up examination.

Tombach (2001) describe 21 patients in a randomized controlled, open-label trial. Patients were classified into two subgroups according to their creatinine clearance: group 1 (*n*=12), eGFR 30 to 80 ml/min/1.73m^2 and group 2 (*n* =9), eGFR<30 ml/min/1.73m^2(Tombach, 2001). Then, patients were randomly assigned to receive the higher dose of 0.3 mmol/kg of the macrocyclic GBCA gadobutrol (group 1, *n*=6/12; group 2, *n*=4/9) or the lower dose of gadobutrol of 0.1 mmol/kg (group 1, *n*=6/12; group 2,*n*=5/9). Changes in vital signs, clinical chemistry, and urinalysis results, including creatinine clearance, were monitored before, at 6 hours, and then every 24 hours until 72 hours (group 1) or 120 hours (group 2) after intravenous injection of gadobutrol.

Tombach (2002) enrolled 11 patients with end-stage renal failure who required haemodialysis treatment (Tombach, 2002). Purpose of the study was to assess the safety and dialysability of gadobutrol. Gadobutrol (1 mol/L) was injected intravenously at randomly assigned doses of either 0.3 or 0.1 mmol of gadolinium per kilogram of body weight for contrast-enhanced MR imaging.

Linear GBCA

Kittner(2007) randomized patients with suspected renal artery stenosis to 0.01, 0.05, 0.1, or 0.2 mmol/kg of the linear GBCA gadodiamide (n=69, 67, 69 and 61, respectively) (Kittner, 2007).Safety of gadodiamide was monitored by comparing the data of 12-lead ECGs, vital signs (blood pressure, body temperature, heart and respiratory rate), serum biochemistry (including renal parameters), and physical examinations collected immediately before and 24 h after gadodiamide administration.

Broome (2007) retrospectively studied the dialysis and MRI records (Broome, 2007). One hundred eighty six dialysis patients underwent 559 MRI exams; including 301 Gd enhanced

MRI between 2000 and 2006. The linear GBCA gadodiamide was the sole Gd chelate used in either 0.1 mmol/kg or 0.2 mmol/kg.

Results

Outcome Post-Contrast Acute Kidney Injury (PC-AKI)

Five studies reported on the incidence of PC-AKI (Kroencke, 2001; Tombach, 2001, Tombach, 2002, Kittner, 2007 and Broome 2007). All five studies reported no cases of PC-AKI, using either linear or macrocyclic GBCA.

Quality of evidence

The quality of certainty of evidence was graded as very low due to high risk of bias (see Table Risk of Bias assessment, downgraded by one point) and the low number of patients (imprecision downgraded by two points).

No studies reported on the outcomes dialysis and mortality.

3. Nephrotoxicity of different gadolinium-based contrast agents

One study investigated the difference in nephrotoxicity between different gadolinium-based contrast agents.

Naito (2017) describes a prospective randomized study including 102 patients that were randomized to either receive 0.1 mmol/kg gadodiamide (linear GBCA) or 0.1 mmol/kg Gd-DTPA (linear GBCA) (Naito, 2017). eGFR in the gadodiamide group was 90.5 +/- 19.5 ml/min/1.73m^2 and 94.1 +/- 26.4 ml/min/1.73m^2 in the Gd-DTPA group. SC was measured 16-80 hour after the procedure. PC-AKI was defined as SC ≥ 44.2 micromol/l or ≥ 30% above baseline.

Results

Outcome Post-Contrast Acute Kidney Injury (PC-AKI)

In both groups, no PC-AKI occurred.

Quality of evidence

The quality of certainty of evidence was graded as very low due to high risk of bias (see Table Risk of Bias assessment, downgraded by one point) and the low number of patients (imprecision downgraded by two points).

No studies reported on the outcomes: dialysis and mortality.

Literature conclusions

Very low GRADE	Administration of macrocyclic gadolinium-based contrast agents does not seem to be associated with an increased risk of PC-AKI. *Sources: (Deray, 2013; Kroencke 2001; Tombach 2001; Tombach 2002)*

Very low GRADE	Administration of linear gadolinium-based contrast agents does not seem to be associated with an increased risk of PC-AKI. *Sources: (Broome 2007; Deray, 2013; Gok Oguz, 2013; Kittner 2007; Naito 2017; Townsend, 2000; Trivedi, 2009)*

Very low	It is unknown whether administration of macrocyclic gadolinium-based

GRADE	contrast agents is associated with an increased requirement of dialysis. *Source: (Deray, 2013)*

Very low GRADE	It is unknown whether administration of linear gadolinium-based contrast agents is associated with an increased requirement of dialysis. *Source: (Townsend, 2000)*

Very low GRADE	There seems to be no dose-response association between macrocyclic gadolinium-based contrast agents and PC-AKI. *Sources: (Kroencke, 2001; Tombach, 2001; Tombach, 2000)*

Very low GRADE	There seems to be no dose-response association between gadolinium-based contrast agents and PC-AKI. *Sources: (Broome 2007; Kittner 2007)*

Very low GRADE	It is unknown whether there is a difference in the risk of PC-AKI between different gadolinium based contrast agents *Source: (Naito, 2017)*

Considerations

Compared to the large amount of literature of the incidence and prevention of PC-AKI after administration of Iodine-based contrast media (ICM), little is known on this subject after administration of GBCA. In general, it is said that GBCA are less nephrotoxic than ICM, and the above-described literature seems to acknowledge that.

It is generally recommendable to use the lowest GBCA dose needed to achieve a diagnostic examination, and usually the standard dose of 0.1 mmol/kg suffices for most clinical indications (ESUR 2017).

Looking more deeply into the chemistry of CM and the results of experimental studies, another picture emerges (Nyman, 2002). First of all, ICM concentrations are expressed in mgI/ml and GBCA concentrations in mmol/ml, a fundamental difference. One mol of Iodine atoms corresponds to 126.9g of I, whereas 1 mol of Gd atoms corresponds to 157.3g of Gd. As most of the commercially available GBCA are 0.5mmol/ml, they thus contain 78.65 mg/ml of Gd. When it comes to Iodine, 0.5mmol/ml I, corresponds to 63mgI/ml. But ICM are usually used in concentrations ranging from 300mg/ml - 400mg/ml, i.e. 2.36mmol/ml - 3.15 mmol/ml. The commercially available iodine doses are thus much higher than the commercially available gadolinium doses (Nyman, 2002).

Furthermore, GBCA contain one attenuating Gd atom per molecule, whereas ICM monomers contain 3 attenuating I atoms per molecule and ICM dimers contain 6 attenuating I atoms per molecule. The combination of more attenuating atoms per molecule and the difference in attenuation of Gd and I at different photon energies, results in the fact that at 120 kVp CT, approximately 110mgI/ml monomer equally attenuates with 0.5mmol/ml Gd. At 80kVp CT, approximately 95mgI/ml monomer equally attenuates with 0.5mmol/ml Gd (Nyman 2002).

For DSA a concentration of 60 to 80mg/ml I monomer, produces the same attenuation as 0.5mmol/l GBCA at commonly used 70-90 kVp range (Nyman, 2002).

Thus, in order to achieve the same amount of attenuation in CT with an ICM monomer 300mg/ml, a triple Gd 0.5mmol/ml dose has to be administered. This also means that DSA attenuation produced by an ICM monomer 300mg/ml is achieved with a 4 - 5 times higher Gd 0.5mmol/ml dose. The above results show that changing from ICM to GBCA in CT and DSA is not a safe option due the 3 to 5 times higher GBCA doses necessary to achieve the same amount of attenuation.

Therefore, the working group concludes that, especially in interventional radiology, using GBCA would potentially lead to more harmful effects compared to ICM, and would not recommend substituting ICM with GBCA. This is in line with a systematic review in which the authors concluded that GBCA does not appear to be safer than iodinated contrast in patients at risk of PC-AKI (Boyden, 2008).

As the dose to achieve significant enhancement for GBCA in MRI is much lower as in CT and DSA, it is not a surprise that the small amount of available literature shows no indication of PC-AKI after the administration of GBCA at the recommend standard dose of 0,1 mmol/kg.

Therefore, the working group sees no additive value in using any prophylactic measures (such as hydration, as described in part 1 of the guideline), and recommends not to use any. A recent Canadian guideline on GBCA in chronic kidney disease states that a standard dose of GBCA in patients with eGFR 30 to 60 is safe and no additional measures are necessary. In patients with eGFR <30 ml/min/1.73m^2 and patients on dialysis, administration of GBCA should be considered individually (Schieda, 2019). Thus an individual risk-benefit analysis with the patient's requesting physician and nephrologist should be made to ensure a strict indication for gadolinium-enhanced MRI with linear agents in patients with eGFR < 30 ml/min/1.73m^2.

Recommendations

Make an individual risk-benefit analysis with the patient's requesting physician and nephrologist to ensure a strict indication for gadolinium-enhanced MRI with linear GBCA in patients with eGFR < 30 ml/min/1.73m^2.

Take optimal CM dosing based on patient weight into account in local dosing protocols for diagnostic MRI examinations.

Do not use prophylactic measures to avoid the development of PC-AKI in high-risk patients (eGFR<30ml/min/1.73m^2) receiving GBCA intravenously at the appropriate dose.

Do not substitute ICM with GBCA in order to avoid PC-AKI in computed tomography and/or digital subtraction angiography.

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Validity and updating

Module[1]	Control holder(s)[2]	Year of authorisation	Next assessment actuality guideline[3]	Frequency of assessing actuality[4]	Who monitors actuality[5]	Relevant factors for changes in recommendations[6]

[1] Name of module
[2] Responsible authors (per module)
[3] Year in which the guideline should be assessed for updating
[4] Time frame: Once every 6 months, one year, two years, five years, or longer
[5] Responsible scientific society
[6] Variety of reasons: new drugs, new therapies, et cetera

Nephrotoxicity of gdolinium based agents	NVvR	2019	2024	5 years	NVvR	New tests or new information on risk factors or preventive measures against PC-AKI after GBCA

Module 7 Risk Factors and Prevention of NSF

Clinical question

7a	Which patients are at-risk for Nephrogenic Systemic Fibrosis (NSF)?
7b	Which measures are necessary to prevent Nephrogenic systemic fibrosis?

Introduction

Nephrogenic systemic fibrosis (NSF) is a very rare, idiopathic, progressive, systemic fibrosis disease that has been associated with renal insufficiency and could result in significant disability due to scleromyxedema-like cutaneous manifestations and mortality. Since there is currently no consistently effective treatment, NSF prevention would be essential, ideally by confirming risk factors for the disease.

Risk factors for NSF

Little is known about the pathophysiology of NSF and it has been postulated that the deposition of free gadolinium causes fibrous connective tissue formation (Ting, 2003). It has been described to occur after exposure to linear gadolinium based contrast agents (GBCA) in particular. Literature published prior to 2007 has not only suggested that free gadolinium, particularly gadodiamide, is a trigger of NSF, but has reported a strong causal relationship between gadolinium exposure and the development of NSF (Thomsen, 2016). However, this association may be affected by other factors or cofactors, such as dosage or type of GBCA, dialysis modality, renal disease severity, liver transplantation, chronic inflammation, or accelerated atherosclerosis.

Prevention of NSF

Several measures to prevent the development of NSF can be taken. As such, the use of high risk and high dose GBCAs should be avoided. An alternative to scanning with GBCA is to scan with the use of iodinated contrast media, however this carries the risk of post-contrast acute kidney injury (see Module 6). Since the connection between NSF and GBCA has become known, changes in CM administration protocols with lower GBCA concentration and use of macrocyclic GBCAs has led to a decrease in NSF incidence. Reports are showing virtually no new NSF cases since 2008 in both patients with normal renal function and patients with renal impairment, in spite of continued use of GBCA, albeit at lower doses and by using preferentially the macrocyclic preparations.

Research question 7a: Risk factors for NSF

Search and selection criteria

To answer the clinical question a systematic literature analysis was performed:
Search question: What factors are related to an increased risk on Nephrogenic systemic fibrosis?

P (Patient):	patients with reduced kidney function or other potential risk factors that are scheduled to receive intravascular contrast media;
I (Intervention):	patients with potential risk factors for NSF: Patient-related, pre-existing chronic kidney disease, Renal insufficiency, chronic CKD, Age 70 years and older, Liver transplantation, Liver failure, Kidney transplantation, Chronic inflammation, Atherosclerosis, Peripheral arterial disease, Dialysis, Renal replacement therapy, Diabetes Mellitus, type 1 or type 2, Congestive heart failure NYHA grade III-IV, Dehydration, Multimorbidity, Concurrent use of nephrotoxic medications: NSAIDs, Cox-2 inhibitors, ACE-inhibitor, ARB-blocker, other Dialysis modality (Peritoneal or

	haemodialysis), Recent dialysis shunt / PD catheter, Acidosis, EPO use, Dose of contrast and type of contrast (GBCA);
C (Comparison):	patients without potential risk factors for NSF;
O (Outcomes):	frequency of NSF, systemic fibrosis, scleroderma, dialysis-associated systemic fibrosis.

Relevant outcome measures

The working group considered nephrogenic systemic fibrosis as a critical outcome measure for the decision making process.

Methods

The databases Medline (OVID) and Embase were searched from January 2000 till February 23th 2018 using relevant search terms for systematic reviews (SRs), randomized controlled trials (RCTs) and observational studies (OBS).

The literature search procured 228 hits: 22 SR, 20 RCTs and 186 OBS. Based on title and abstract a total of 20 studies were selected. After examination of full text 19 studies were excluded and 1 study involving linear GBCAs was included in the literature summary. No studies were identified involving macrocyclic GBCAs, which are currently the only agents available in the European market.

Summary of the literature

Studies that assessed risk factors related to administration of type and dose of gadolinium-based contrast agents (GBCA) have been described in the module nephrotoxicity of gadolinium-based contrast agents. There was 1 additional study included investigating other potential factors associated to NSF. Kallen (2008) performed a matched case-control study (19 cases and 57 controls), however this study was restricted to linear GBCAs only. Participants were dialysis patients with and without a diagnosis of NSF treated at an academic medical centre.

Results

Outcome- comorbidities

In a multivariate analysis Kallen (2008) found no association between NSF and selected exposures (history of hypothyroidism (OR, 95% CI: 4.18 0.66 to 26.57); history of deep venous thrombosis (OR, 95% CI: 3.37 0.60-18.85), and dependent oedema (OR, 95% CI: 3.15 0.67 to 14.77).

Quality of evidence

The quality of certainty of evidence was downgraded from high to very low: downgraded by two levels due to imprecision (small number of patients), and indirectness (NB. only linear GBCAs were administered to the patients in the study which are no longer available on the European Market).

Research question 7b: Prevention of NSF

Search and selection criteria

To answer the clinical question a systematic literature analysis was performed for the search question: What is the effect of the different measures to prevent nephrogenic systemic fibrosis in patients who have an increased risk of developing nephrogenic systemic fibrosis and who receive contrast with gadolinium?

P (Patient): patients exposed to gadolinium-based contrast agents who have an increased risk of developing nephrogenic systemic fibrosis (NSF);
I (Intervention): measures for prevention of NSF;
C (Comparison): no measures or other measures for prevention of NSF;
O (Outcomes): nephrogenic systemic fibrosis (NSF), mortality.

Relevant outcome measures
The working group considered Nephrogenic systemic fibrosis (NSF) and mortality as critical outcome measures for the decision making process.

Methods
The databases Medline (OVID) and Embase were searched from January 1996 till March 23th 2018 using relevant search terms for systematic reviews (SRs), randomized controlled trials (RCTs) and observational studies (OBS).

The literature search procured 142 hits. 7 SR, 10 RCTs, 43 OBS, and 82 other types of studies. Based on title and abstract a total of 29 studies were selected. After examination of full text all studies were excluded and no studies have definitely been included in the literature summary.

Summary of the literature
Not applicable. There were no studies investigating the research question and meeting the selection criteria.

Literature conclusions

Very low GRADE	There seems to be no association between co-morbidities (history of hypothyroidism or deep venous thrombosis, and dependent oedema) and risk of nephrogenic systemic fibrosis in patients on dialysis receiving linear GBCAs. *Source: (Kallen, 2008))*

Considerations
Prevalence and risk of NSF and type of GBCA
The majority of histology proven NSF cases has been described between 1997 and 2007, which largely consisted of cases with a temporal relation with high dose linear gadolinium-based contrast agent (GBCA) administrations (Attari, 2019). Several meta-analysis have shown a positive correlation between GBCA and NSF, predominantly based on studies using linear GBCA (Agarwal, 2009; Zhang, 2015). The risk of NSF relate to the administered dose and physiochemical characteristics of GBCAs, including pharmacodynamic stability, kinetic stability, and the amount of excess ligand (Khawaja, 2015).

In a risk-factor analysis of 370 biopsy-proven published NSF cases following use of linear GBCA it was concluded that reductions in risk may be attained with: 1) avoiding high doses of GBCA (> 0.1 mmol/kg); 2) avoiding nonionic linear GBCA in patients undergoing dialysis and patients with eGFR < 30 ml/min/1.73m^2, especially in the setting of pro-inflammatory conditions; 3) dialyzing quickly after GBCA administration for patients already on dialysis; and 4) avoiding GBCA in acute renal failure (Zou, 2011).

By combining pharmacovigilance (Food and Drug Administration Adverse Event Reporting System (FAERS)) and legal databases, a total of 382 biopsy-proven, product-specific cases of

NSF were analysed. Of these, 279 cases were unconfounded and all involved a linear GBCA, nonionic more than ionic, and most frequently gadodiamide. No unconfounded cases were found for gadoteridol or gadobenate (Edwards, 2014).

A very recent study based on a legal database containing biopsy-proven, unconfounded NSF cases has estimated that a total of 197 and 8 cases have been reported for the linear GBCAs gadodiamide and gadoversetamide, respectively. Estimated incidences of NSF based on the FAERS analysis are 13.1/million and 5.0/million administrations for the linear non-ionic GBCAs gadodiamide and gadoversetamide worldwide (Semelka, 2019).

Considering the hypothesized pathophysiology of NSF involving free circulating gadolinium ions, macrocyclic GBCAs are considered to have a higher thermodynamic and kinetic stability and thus less associated with the risk of NSF (Sherry, 2009).

The prevalence of NSF after use of macrocyclic GBCA is very low. No cases of NSF have been found in large studies using gadobenate (Bruce, 2016), gadobutrol (Michaely, 2017), and gadoteridol or gadobenate (Soulez, 2015). Using the Girardi criteria for diagnosis, the worldwide total number of unconfounded cases for gadobutrol is 3 (Elmholdt, 2010; Endrikat, 2018), while there were no cases for gadoteridol (Reilly, 2008; Edwards, 2014), or gadoterate (Soyer, 2017).

In addition, there have been no unconfounded cases reported for the hepatobiliary linear GBCA gadobenate (Edwards, 2014) and gadoxetate (Endrikat, 2018). Patients with chronic liver diseases that are awaiting or undergoing liver transplantation are no longer consider to be an independent risk factor for NSF (Smorodinsky, 2015).

On March 17, 2016, the European Medicines Agency (EMA) initiated a review of the risk of gadolinium deposition in brain tissue following the repeated use of GBCAs in patients undergoing contrast-enhanced MRI scans. Following an in-depth review, the EMA issued its final recommendations on July 21, 2017, endorsed by the European Commission on November 23, 2017, and now applicable in all EU Member States limiting the use of GBCAs to macrocyclic GBCAs and restricting the use of linear GBCAs to selected indications, such as hepatobiliary MRI or MR arthrography (EMA, 2017; Dekkers, 2018). See Table 7.1 for overview of GBCAs and recommendations of the EMA.

Table 7.1 Overview of available GBCAs and the EMA recommendation (Dekkers, 2018)

Name	Ligand	Structure	Ionicity	EMA recommendation
Gadopentetate	DTPA	Linear	Ionic	**Suspend (maintain for intra-articular injections only)**
Gadobenate	BOPTA	Linear	Ionic	**Restrict to liver scans**
Gadoxetate	EOB-DTPA	Linear	Ionic	Maintain (for liver scans)
Gadodiamide	DTPA-BMA	Linear	Non-ionic	**Suspend**
Gadoversetamide	DTPA-BMEA	Linear	Non-ionic	**Suspend**
Gadoterate	DOTA	Macrocyclic	Ionic	Maintain
Gadoteridol	HP-DO3A	Macrocyclic	Non-ionic	Maintain
Gadobutrol	BT-DO3A	Macrocyclic	Non-ionic	Maintain

Considering these new regulations, previous perceived risks for NSF based on linear GBCAs should be differentiated from the risks that apply to macrocyclic GBCAs. From the data currently available, for the GBCA currently allowable in Europe the risk of NSF is extremely low, even in patients with eGFR < 30 ml/min/1.73m^2 and patients on dialysis.

Haemodialysis to prevent NSF

Several studies have been performed to investigate the dialysability of GBCAs. These studies have shown that a single haemodialysis session can remove around 65-97% of circulating GBCA, whereby success depends on dialysis technique (high flux, large pore membranes (Ueda 1999)). Approximately 98% is eliminated after three consecutive dialysis sessions (Joffe 1998; Tombach 2002; Gheuens 2014). Based on these data, early haemodialysis would be an effective treatment for preventing NSF. However, this hasn't been proven. For example, a retrospective chart review described ten haemodialysis patients who developed NSF after administration of GBCA. In none of these patients, immediate haemodialysis after injection with GBCA could prevent NSF (Broome 2007).

Based on the dialysability of GBCAs and the fact that NSF is a potential lethal condition, many guidelines recommend scheduling GBCA administration shortly before the next haemodialysis session (ACR Manual 10.3; ESUR Guideline v10).

Peritoneal dialysis does not effectively remove gadolinium (Rodby 2018). However, instituting haemodialysis in a peritoneal dialysis patient without a functioning vascular access goes with a significant risk, as it is an invasive treatment that requires placement of a temporary haemodialysis catheter. The same accounts for predialysis patients (eGFR<15 ml/min/1.73m^2).

Recommendations

Use low-risk (ionic and non-ionic) **macrocyclic** GBCAs for medical imaging in all patients. Linear GBCAs have been associated with NSF, therefore, consider **linear** agents only if a macrocyclic agents cannot answer the diagnostic question.

Make an individual risk-benefit analysis with the patient's requesting physician and nephrologist to ensure a strict indication for gadolinium-enhanced MRI using **linear** agents in patients with eGFR < 30 ml/min/1.73m^2.

For prevention of NSF in patients who are already dependent on haemodialysis or peritoneal dialysis, the administration of **macrocyclic** GBCA does not have to be followed by an immediate haemodialysis session.

To limit the amount of circulating GBCA, in hemodialysis patients the administration of **linear** GBCA should be followed immediately by a (high-flux) haemodialysis session, which is repeated on the following two days.

In predialysis patients (eGFR<15 ml/min/1.73m^2) and peritoneal dialysis patients, the risk of NSF due to **linear** GBCA should be weighed against the risk of placement of a temporary haemodialysis catheter.

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Guideline Module Validity and Maintenance

Module[1]	Responsible authors[2]	Authorisation Year	Next evaluation of validity of guideline	Frequency of evaluation of validity[3]	Who surveys the actuality of this guideline[4]	Relevant factors for changing recommendations[1]

[1] Name of module
[2] Responsible authors (per module)
[3] Time frame: Once every 6 months, year , two years, five years, longer
[4] Responsible scientific society

Risk factors and prevention of NSF	NVvR	2019	2024	5 years	NVvR	New information on risk factors for NSF or treatment/prevention options

[5] Variety of reasons: new drugs, new therapies, et cetera

Module 8 Gadolinium Deposition in the Body and T1w Hyperintensity in the Brain

Clinical question

What is the clinical relevance of gadolinium-based contrast agent (GBCA) induced T1w hyperintensity of the nucleus dentatus and the globus pallidus in the brain?

Introduction

In 2014, Kanda observed progressive unenhanced T_1-weighted (T_1w) signal intensity (SI) increases in the dentate nucleus and globus pallidus in patients who received at least 6 doses of Gadolinium (Gd) chelates (Kanda, 2014). This publication triggered a huge amount of research on this subject, which is still going on today. Weekly, new publications arise, which make it impossible to give an up to date overview in this guideline. The broad outlines of gadolinium deposition will be discussed.

Search and selection criteria

To answer our clinical question a systematic literature analysis was performed. This was an orientatational search, to examine the clinical relevance of the T1w hyperintensity of the nucleus dentatus and the globus pallidus.

P (Patient):	patients who have repeatedly received gadolinium-based contrast agents and have signs of gadolinium retention such as T_1w hyperintensity of the nucleus dentatus and the globus pallidus, but also gadolinium retention in the bones, liver and skin;
I (Intervention):	not applicable;
C (Comparison):	not applicable;
O (Outcomes):	signal intensity, signal increase, hyperintensity, hypersignal. Central torso and peripheral arm and leg pain. Distal arm and leg skin thickening. Rubbery subcutaneous tissues. Clouded mentation or brain fog.

Relevance of outcome measures

Signal intensity, signal increase, hyperintensity, hypersignal were considered critical outcomes and central torso, peripheral arm and leg pain, distal arm and leg skin thickening and rubbery subcutaneous tissues and clouded mentation or brain fog were considered important outcome measures.

Methods

The databases Medline (OVID), Embase and the Cochrane Library were searched from 1st of January 1996 to 11th of November 2018 using relevant search terms for systematic reviews (SRs), randomized controlled trials (RCTs) and observational studies (OBS).

The literature search produced 722 hits. A total of 99 abstracts were selected. When the full texts were examined, none of them fulfilled the selection criteria. Based on this, it was concluded that no conclusions on the clinical aspect could be drawn. Based on the literature, the narrative review shown below was written by the guideline committee.

Summary literature

Not Applicable

Results
Not Applicable.

Literature conclusions
Not applicable.

Considerations
The following is a short overview of the current state of gadolinium retention in the brain and body. See also the Introduction to Safe Use of Gadolinium-Based Contrast Agents.

Increased SI due to Gd deposition
Two autopsy studies, both published in 2015, showed that the increased SI on T_1-weighted sequences (T_1w) in the dentate nucleus and globus pallidus was indeed due to the presence of retained Gd (Kanda, 2015; McDonald, 2015). The majority of the Gd was localized in the perivascular spaces (4), whereas a much smaller fraction crossed the blood-brain barrier and was situated in the neural interstitium and cellular organelles (Fingerhut, 2018; McDonald 2015; McDonald, 2017_1; McDonald, 2017_2).

Difference between linear and macrocyclic chelates
Subsequent studies confirmed progressive T1 SI increases after intravenous administration of linear GBCA (Errante, 2014; Kanda, 2015_1; Radbruch, 2015; Ramalho, 2015; Quattrocchi, 2015; Quattrocchi, 2015_1). The majority of the publications do not show dose-dependent changes in T1w SI after macrocyclic GBCA exposure (Cao, 2016; Kanda, 2015_1; Kromrey, 2017; Radbruch, 2017; Ramalho, 2015; Quattrocchi, 2015_1; Tibussek, 2017). Others report a weak T1w SI increase after administration of macrocyclic GBCA (Bjornerud, 2017; Kang, 2018; Rossi, 2017; Spelndiani, 2018; Stojanov, 2016;). A study of human brain tissue demonstrated measurable Gd after single dose intravenous administration of both linear and macrocyclic chelates (Murata, 2016). Significant less Gd retention was observed after macrocyclic chelate exposure, compared to linear chelate exposure (Murata, 2016).

These results led to a European Medicines Agency (EMA) directory regarding GBCA, stating to suspend the use of linear GBCA in order to prevent any risks that could potentially be associated with Gd brain deposition (EMA's final opinion confirms restrictions on use of linear gadolinium agents in body scans, 2019). Only the liver specific linear GBCA gadoxetate and gadobenate are allowed to be used in these situations where they meet a specific diagnostic need (EMA's final opinion confirms restrictions on use of linear GBCA in body scans, 2017).

Gd deposition in other tissues than brain.
Besides the brain and skin in patients with NSF, Gd retention has been reported in many other tissues including the bone, muscles, tendons, nerves, blood vessels and visceral organs (Gibby, 2004; Murata, 2016; Sanyal, 2011).

Pathophysiology of Gd deposition
Stability of Gd chelates is determined by their thermodynamic and kinetic stability. Thermodynamic stability of a chemical system means that this system is neither consuming nor releasing heat, i.e. thermal energy. In the absence of a change in thermal energy, the system is not undergoing a chemical reaction. Kinetic stability refers to the fact that a chemical reaction can occur at a certain speed. If a chemical system is kinetically stable, it means that reactions within this system occur very slowly. In general, macrocyclic GBCA have higher thermodynamic and kinetic stability constants and are therefore more stable

than linear Gd chelates and therefore release less amount of Gd^{3+} out of the chelate (McDonald, 2018). Very little is known about the fate of free Gd^{3+} within the human body, and how biologically active and potentially toxic chemical forms of retained Gd in tissues are formed (McDonald, 2018). After intravenous injection in patients with normal kidney function, 73% to 99% of the dose is excreted within 24 hours after injection. Biodistribution data of GBCA suggest the presence of a longer lasting phase of residual excretion from other tissues, from which Gd is slowly eliminated (McDonald, 2018). The potential toxicities of this small pool of retained Gd are largely unknown (McDonald, 2018).

Clinical importance of Gd deposition

After hundred millions of Gd chelate administered doses, 139 patients with normal or minimally impaired kidney function reported effects that they associate with Gd exposure. The symptoms include chronic pain, fatigue, dermal changes, musculoskeletal disturbances, cognitive impairment, and visual impairment (Burke, 2016). An association between these symptoms and Gd chelate exposure has been postulated and the term "gadolinium deposition disease" has been proposed (Semelka, 2016). The Food and Drug Administration (FDA) could not find a causal relationship between Gd deposition and symptoms. If Gd deposition is associated with clinical harm, the harm is likely to be rare or occult for the vast majority of exposed patients (McDonald, 2018).

Future directions

Today, many question marks exist when it comes to the explanation of how Gd deposition occurs and what the clinical consequences, if any, are. In 2018, a research roadmap on Gd deposition was proposed, with the highest priorities to determine a) if Gd deposition adversely affects the function of human tissues, b) if deposition is causally associated with short- or long-term clinical manifestations of disease and c) if vulnerable populations are at greater risk for developing clinical disease (McDonald, 2018).

Recommendations

Ensure a strict indication for gadolinium-enhanced MRI and use EMA-approved GBCA in all patients to minimize possible gadolinium deposition.

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Guideline Module Validity and Maintenance

Module[1]	Responsible authors[2]	Authorisation Year	Next evaluation of validity of guideline	Frequency of evaluation of validity[3]	Who surveys the actuality of this guideline[4]	Relevant factors for changing recommendations[5]
GBCA deposition	NVvR	2019	2021	2 years*	NVvR	New information on GBCA deposition

***Note: This topic will be covered in more detail in Safe Use of Contrast Media, part 3.**

[1] Name of module
[2] Responsible authors (per module)
[3] Time frame: Once every 6 months, year , two years, five years, longer
[4] Responsible scientific society
[5] Variety of reasons: new drugs, new therapies, et cetera

Module 9 Safe use of Central Venous Catheters, Haemodialysis Catheters, Peripherally Inserted Central Catheters, and Totally Implantable Venous Access Devices for contrast administration using power injectors

Research question

How can central venous catheters (CVC), haemodialysis catheters (HC), peripherally inserted central catheters (PICC), and totally implantable venous access devices (TIVAD) be safely used for the administration of intravenous contrast agents, particularly using power injectors and higher injection rates for obtaining high-quality images?

Introduction

Power injection of contrast through CVCs, HCs, PICCs, and TIVADs holds a risk for device failure and secondary contrast extravasation. The exact method how to "power-inject" with respect to applied pressure limitations remains part of local practice guidelines combined with the central catheter line manufacturer's instructions.

Search and select criteria

A systematic literature analysis was performed to answer the research question: How can central venous catheters (CVC), haemodialysis catheters (HC), peripherally inserted central catheters (PICC), and totally implantable venous access devices (TIVAD) be safely used for the administration of intravenous contrast agents, particularly using power injectors and higher injection rates for obtaining high-quality images?

P (Patient):	patients with central venous catheters (CVCs) or Peripheral inserted central catheters (PICCs) and an indication for administration of iodine-based contrast for performing computed tomography examinations;
I (Intervention):	non-tunneled central venous catheters (CVCs), tunneled CVCs, implantable ports, peripherally inserted central catheters (PICC).
C (Comparison):	normal Venflon, normal peripheral infusion;
O (Outcomes):	failure contrast media examination, contrast extravasation, failure of examination, damaged CVCs or PICCs, complication rates, device failure, and device dwell times.

Relevance of outcome measures

The working group considered the outcomes failure of contrast media examination, complication rates (damaged CVCs or PICCs, contrast media extravasation) critical measures and outcome for the decision making process. The working group did not define criteria for outcomes a priori, but used the outcomes as defined in the studies.

Methods

The databases Medline (OVID), Embase and the Cochrane Library were searched from 1st of January 1996 to March 2018 using relevant search terms for systematic reviews (SRs), randomized controlled trials (RCTs) and observational studies (OBS). A systematic literature search was conducted at May 16th 2018.

The literature search produced 97 hits: 2 SR, 13 RCTs and 13 OBS and 68 mixed designs. Based on title and abstract a total of 18 studies were selected. After examination of full text 0 articles were selected. Since there are no direct comparisons on the safety or efficacy of contrast injections via central venous catheters or peripheral inserted central catheters

(PICCs) versus normal infusion, literature has been described in a descriptive manner. The SR of Buijs, 2017 was selected and covers the literature on efficacy and safety of contrast injection via central venous catheters for contrast enhanced computed tomography until September 10th 2016. This study was used as key article for the literature review. Studies published after September 10th 2016, on efficacy and safety of contrast injection via central venous catheters or peripheral inserted central catheters were added.

Summary literature

Buijs (2017) described a systematic literature review on the efficacy of contrast injection via central venous catheters for contrast enhanced computed tomography. A search query was built by linking two content areas: 'central catheter' and 'contrast enhanced' with relevant synonyms for both areas. Publications were selected, describing original research on the use of CVCs for contrast administration for CT-scans focusing on safety, efficacy, and complications. Exclusion criteria included: no full-text available, publication not written in English or Dutch, review articles, case reports, and studies focusing on the use of CVCs in paediatrics. Two independent assessors screened titles and abstracts for full-text selection. Studies were classified as having low risk of bias if they satisfied all criteria and high risk of bias if they satisfied less than three criteria. The remaining studies were classified as having a moderate risk of bias. (See risk of bias assessment). Frequencies of complications were extracted from the selected studies were tabulated and presented as percentages. Data on quality of images was extracted where applicable. Twenty-three articles were considered eligible for answering the research question after selection based on title and abstract. Seventeen articles were excluded during full text screening. During cross-referencing, one study was included missed by the initial search (Carlson, 1992; Goltz, 2011). Eventually, eight studies were included for critical appraisal (Coyle, 2004; Goltz, 2011; Herts, 2001; Lozano, 2012; Macht, 2012; Morden, 2014; Sanelli, 2004). Carlson (1992) evaluated the system pressure in thirteen patients with a Port-A-Cath. The pressure measurement was not standardized: five patients' injection pressures were measured with a pressure gauge that was placed in-line during injection and eight patients' injection pressures were not. The lack of standardization and limited relevance led to the exclusion of this study. Finally, seven studies were included for further analysis (Coyle, 2004; Goltz, 2011; Herts, 2001; Lozano, 2012; Macht, 2012; Morden, 2014; Sanelli, 2004). Table 9.1 presents study characteristics and main outcome measures on safety and image quality. Individual outcome measures among studies on safety and efficacy are described separately.

Table 9.1 Study characteristics and main findings for complications and image quality

Study (year)	N	Study	Type catheter	Injection rate and peak pressure	Safety	Image quality
Central Venous Catheters						
Herts, 2001	174 versus. 51 peripheral	RCT	117 port-type, 41 3L, 10 DL, 6 unknown	CVC: 1.5–2 mL/s, pressure cut-off 100 psi Peripheral: 2.5–3 mL/s, pressure cut-off 300 psi	1 (0.6%) CVC no longer patent1 positive blood culture	Less contrast enhancement in thoracic aorta, pulmonary artery, liver in CVC group
Macht, 2012	104	Retrospective	Distal 16G lumen of Arrow multi-lumen (3L, 5L)	3L: 4.4 ± 0.5 mL/s; 200.7 ± 17.5 psi5L: 4.6 ± 0.6 mL/s; 194.5 ± 6.5 psi	No complications	-
Sanelli, 2004	104	Prospective	Arrow multi-lumen CVC (n = 89) Percutaneous sheaths IJV (n =15)	3 mL/s (n =15); 4 mL/s (n =8); 4 mL/s (n = 79); 5 mL/s (n = 2) Pressure limit 300 psi; 5/43 pressure-limited (306–316 psi)	13/60 (21,7%) blood cultures positive during ICU course	-
Peripherally Inserted Catheters						
Coyle, 2004	110	Prospective	12 SL 5F PICC 98 DL 5F PICC	1–2 mL/s (n = 8), 2 mL/s (n =89), 2–3 mL/s (n = 9), 4 mL/s (n = 4) SL: 16–79 psi, DL: 40–135 psi.	2 (1.8%) ruptured 1 balloon (DL, 4 mL/s)	81 average; 23 above average; 6 below average
Lozano, 2012	78	Prospective	Power injectable PICC (4–6F, SL/DL)	Mean injection rate 4.13 ± 0.855 mL/s (range 3–5); pressure limit 300 psi	12/78 (15.4%) dislocation	-
Morden, 2014	243 high rate versus. 138 rate increase	Retrospective	CT-PICC (4–6F, SL/ DL/3L)	Injection rates 2–5 mL/s Pressure limit 300 psi	20/243 (8.2%) displaced versus. 3/138 (2.2%)	-
Totally Implantable Venous Access Devices						
Goltz, 2011	141 versus. 50 peripheral catheter	Retrospective	141 TIVAP forearm	TIVAP: Max 1.5 mL/s; mean pressure 121.9±24.1 psi Peripheral: 3 mL/s, pressure limit 300 psi	1 (0.7%) dislocation with rupture3 (2.1%) suspected systemic infection <4 weeks	31/44 (70.4%) trigger threshold not reached Significant higher aortic contrast via peripheral catheter

Legend: CVC =central venous catheter, SL= single lumen, F= French, PICC= peripherally inserted central catheter, DL= double lumen, TIVAP= totally implantable venous access port, 3L= triple-lumen, G= gauge, 5L= quintuple-lumen, IJV= inferior jugular vein, ICU= intensive care unit.

Results

1. Complications following contrast injection via central catheters

Central Venous Catheters (CVC)

Herts (2001) randomized 225 patients, after reassignment because of inability to obtain access, in a central venous access group (n= 174) and a peripheral venous access group (n= 51). No significant differences in early, delayed, and late complications were found. In the central venous access group, one (1/174; 0.6%) patient reported that her device was no longer patent, while being successfully used for chemotherapy after contrast injection. In one (1/174; 0.6%) patient an infection was reported. Macht (2012) and Sanelli (2004) implemented a strict safety protocol, in which they verified the correct position of the CVC in the superior vena cava (SVC) on scout view before contrast injection, checked for adequate blood return, and checked the patency of the catheter afterwards. They did not report complications relating to the injection using the CVC.

Peripherally inserted catheters (PICC)

Coyle (2004) found two (2/110; 1.8%) externally ruptured PICCs while injected at a rate of 2 mL/sec. Ruptures were caused by mechanic obstructions; i.e. one of the ruptured PICCs was clamped, the other kinked at the venous entry site. Another PICC ballooned without rupturing and further injected was stopped.

Lozano (2012) evaluated the frequency of displacement of power-injectable PICC (PI-PICC) after contrast injection. Correct catheter position was defined as cephalic to or caudal to the right tracheobronchial angle. A total of 12/78 (15.4%) PI-PICC tips changed in position after injection of contrast medium. Seven displaced toward the brachiocephalic veins. They found that PI-PICCs positioned in the proximal SVC (cephalic to tracheobronchial angle) before contrast administration had a higher risk of displacement compared to catheters positioned in the distal SVC (caudal to tracheobronchial angle) before contrast administration (5/8 (62.5%) versus 7/69 (10.1%)). Distal location in the SVC decreased this risk by 89% (RR= 0.11; 95%CI= (0,026; 0,487); p= 0.006).

Morden (2014) evaluated a rate increase technique of the saline flush after contrast injection via power-injectable PICCs (PI-PICC), in which they started with a saline flush at 2 mL/s and progressively increased to the rate of contrast injection. With this technique, they found a lower percentage of PI-PICC tip displacement (20/243 (8.2%) without rate increase technique versus. 3/138 (2.2%) with rate increase technique).

Totally Implantable Venous Access Devices (TIVAD)

Goltz (2011) evaluated power injections in 141 patients with totally implantable venous access ports (TIVADs) in their forearm. One (1/141; 0.7%) TIVAD catheter tip was dislocated into the brachiocephalic vein and revealed a catheter rupture during an interventional retrieval attempt. Three (3/141; 2.1%) catheter tips were suspected of a systemic infection within four weeks.

2. Contrast enhancement and image quality

Central Venous Catheters (CVC)

In Herts (2001), two reviewers who were blinded for route of injection measured the enhancement of the large vessels. The level of enhancement of the thoracic aorta, pulmonary artery, and liver vasculature was significantly less dense in the central venous access group compared to the peripheral venous access group. No significant difference was seen in the enhancement of the abdominal aorta.

Totally Implantable Venous Access Devices (TIVAD)
In Coyle (2004) CT images were assessed subjectively by the radiologist supervising the CT examination, which resulted in categorizing the quality of CT images as average in 81/110 (74%) of cases and above average in 23/110 (21%) of cases.

Goltz (2011) found a significantly lower arterial contrast density in patients with TIVADs compared with classic peripheral cannula, resulting in limited image quality. In 31/44 (70.4%) examinations, manual initialization was necessary, while initial arterial bolus tracking was performed, because the trigger threshold had not been reached in time. This might be the result of the lower flow rate of 1.5 mL/s through TIVADs. Triggering with automatic scan initiation resulted in significantly higher contrast in the aorta compared to manual scan initiation (163 HU versus 144 HU, p =0.039).

Quality of evidence
The quality of certainty of evidence was graded as very low due to high risk of bias (see Table Risk of Bias assessment, downgraded by one point) and low number of patients (imprecision, downgraded by two points) and lack of studies where a control group was present.

Literature conclusions

Very Low GRADE	The frequency of complications following contrast injection via CVCs, without safety protocols, varies from 0,6% to 15,4% across studies. *Sources: (Coyle, 2004; Goltz, 2011; Herts, 2001; Lozano, 2012; Morden, 2014)*

Very Low GRADE	It seems that contrast injections via CVCs are a safe alternative to peripheral injection if safety protocols are followed. *Sources: (Coyle, 2004; Goltz, 2011; Herts, 2001; Lozano, 2012; Morden, 2014)*

Very Low GRADE	There were no complications reported following contrast injection via CVCs when strict safety protocols were implemented. *Sources: (Macht, 2012 and Sanelli, 2004)*

Very Low GRADE	Safety protocols are warranted when contrast injections are performed via central venous catheters, and should include aspirating blood before injecting contrast media, localizing the CVC before and after injection, making sure no kinking of the CVC and attached lines occurs, using sterile syringes, and making sure the CVC is patent after scanning. *Sources: (Macht, 2012 and Sanelli, 2004)*

Very Low GRADE	It is unknown whether contrast injections via CVCs result in successful contrast media examination as quality of scans varies among studies. *Sources: (Coyle, 2004; Goltz, 2011 and Herts, 2001)*

Very low. GRADE	It seems that power injectable PICCs positioned in the proximal SVC (cephalic to tracheobronchial angle) before contrast administration had a higher risk of displacement compared to catheters positioned in the distal SVC (caudal to tracheobronchial angle) before contrast administration. *Source: (Lozano, 2012)*

Considerations

A patent intravenous access site is needed for the administration of intravenous contrast through power injection in order to obtain high quality contrast enhanced or angiographic images. Local hospital guidelines should be available to guide the proper and safe administration technique for the applied contrast medium, but these a frequently limited to peripheral venous injection only. Possible complications of IV contrast injection are: contrast medium extravasation, air embolism, catheter rupture, catheter weakening, and loss of catheter patency.

With the use of power injectors, injection pressure is also a function of the injected CM. In general, the use of lower concentrations of the CM, low viscosity of the CM, and high temperature of CM are beneficial to keep injection pressures as low as possible (Macha, 2009; Kok, 2014).

There are only a limited number of studies that compare the safety and efficacy of different venous access sites. No difference is reported in patency between CVCs or peripheral venous access catheters, however there seems to be a difference in the level of the contrast enhancement of large vessels, which affects the image quality in favour of a peripheral venous access. A short peripheral IV catheter in the antecubital or forearm is therefore the preferred route for contrast administration. However other routes may be needed and each is considered separately below.

<u>Central Venous Catheters (CVC)</u>

In the comparative studies, there is no difference in reported complications in terms of patency related to the contrast medium power injection compared to peripheral venous access sites. However, image quality is limited compared to peripheral venous access sites.

Herts (Herts, 1996) also performed an in vitro study with 10F Hickman and Leonard CVCs, and found that CM, flow rate and catheter type were main determinants of peak injection pressures. The peak injection pressures remained well within manufacturer limits of 25 psi (175 kPa).

In an in vitro study with a 3-lumen 16G (4.9F) Arrow CVC, a significant safety margin was shown for CVCs, with bursting pressures depending on catheter dwell time, 262 PSI for new and 213 PSI for used catheters. Lowest flow rate associated with bursting was 9 ml/s. Ruptures occurred always *outside* the patient (Macha, 2009). Similar high bursting pressures were seen in other studies. A study using 3-lumen 16G CVCs showed pressure to be above 175 PSI, whereas high flow injections 4,5 to 7,0 ml/s were associated with injection pressures of 48 to 81 PSI (Beckingham, 2017). An older study found no catheter failures at flow rates of 5 to 25ml/s with an even higher bursting pressure of 920 psi (Zamos, 2007).

To help prevent the rupture of vascular access devices when they are used with power injectors, the FDA long ago has already issued recommendations (FDA, 2004).

Users of central vascular access devices should:

1 Check the labelling of each vascular access device for its maximum pressure and flow rate. If none is provided, assume device is NOT intended for power injection and do not use.
2 Know the pressure limit setting for your power injector and how to adjust it.
3 Ensure that the pressure limit set for the power injector does not exceed the maximum labelled pressure for the vascular access device(s).

Haemodialysis Catheters (HC)

There are no patient controlled studies available that compare the usability and safety of dialysis catheters for IV contrast administration through power injection versus peripheral IV catheters or central venous catheters.

However, haemodialysis catheters have larger diameters than other venous catheters. An in vitro study on cuffed and non-cuffed catheters for haemodialysis showed that pressure inside the catheters (14,0 ± 3,3 PSI) was 23x lower than the pressures indicated by the power injectors (338 ± 8,7 PSI). It is believed that the high pressures in the injector are mainly caused by the long, small calibre connection tubing that connects the injector to the HC (Hollander, 2012). Therefore, their use for power injection should be safe when adhering to the recommendations of the manufacturer.

Adjustments to the scan protocol may be needed to preserve optimal image quality. Especially in chronic dialysis patients with poor vascular conditions vein preservation has a high priority.

Peripherally inserted catheters (PICC)

Spontaneous migration of PICCs is a known complication in 1.5 to 3% with multifactorial aetiology (Seckold, 2015). Multiple other case series have confirmed that the catheter tip of power-injectable PICCs can migrate due to the power injection during CT (Lambeth, 2012; Craigie, 2018).

Tubing ruptures during power injection are reported when there is a mechanical obstruction such as a clamped port or kinking of the line. Silicone catheters are have higher failure rates than polyurethane catheters and are unsuitable for power injection (Salis, 2004).

Strict protocols are recommended to check its position via CT scout/scanogram radiograph before and after power injection during CT, and to check patency of the catheter after CM injection.

Totally Implantable Venous Access Devices (TIVAD)

A retrospective analysis of TIVADs with silicone catheters showed a 3.4% rate of complications (Busch 2012; Busch, 2017). Newer power-injectable TIVADs have a high patient satisfaction rate and with no device failures during power injections (Alexander, 2012; Chang, 2013).

There are no data on catheter tip migration in TIVADs, mainly because they are tunneled catheters inserted surgically with a deep position of the catheter tip. Theoretically, for devices with high positions of the catheter tip, the same risks for migration as in PICCs would exist.

The GAVeCeLT group formulated already in 2011 recommendations to prevent complications with TIVADs and recommends only using systems specifically suitable for power injection with adequate check of catheter position (Bonciarelli, 2011.

A Canadian study on CT image quality showed that contrast injection via a CVC or port system has equivalent image quality when compared to conventional peripheral intravenous injection technique. (Haggag, 2016)

Recommendations

Note: High quality of imaging is generally needed for low-contrast situations, such as in staging studies in brain, head & neck, hepatobiliary, genitourinary or colorectal imaging. Lower quality may be acceptable for high-contrast situations such as in follow-up studies of lymph nodes (lymphoma, testicular cancer) or in pulmonary or musculoskeletal imaging.

Use a power injector and a peripheral venous access catheter for IV contrast media administration to obtain the best level of quality of contrast-enhanced imaging, especially in low-contrast situations (see Note).

When a peripheral venous catheter is unavailable: Check the position of the CVC, TIVAD, or PICC line and its patency before and after the power-injected contrast administration.

Power-injectable central venous catheters may be safely used for administration of CM using a power injector, when recommendations of the catheter manufacturer are followed.

Power-injectable haemodialysis catheters may be safely used for administration of CM using a power injector, when recommendations of the catheter manufacturer are followed.

Especially in haemodialysis patients, vein preservation should weigh heavily in the choice of access for CM administration. When the use of a peripheral vein for contrast administration in haemodialysis patients is inevitable, the veins in the elbow fold should be used as much as possible. If this is impossible, veins on the back of the hand or the use of dialysis fistula for contrast administration should be considered in consultation with a nephrologist.

There is a risk of catheter tip migration of PICCs and TIVADs when CM is injected via a power injector in patients with a catheter tip position above the tracheobronchial angle.

When a power-injectable PICC or TIVAD is used for CM administration, check the position of the catheter tip with DX, CT or fluoroscopy before and after power-injection of CM.

When a power-injectable CVC, HC, PICC or TIVAD is used for CM administration with a power injector, check the patency of the catheter after the procedure by manual flush of 20ml normal saline.
When a power-injectable HC is used for CM administration, immediately after power-injection a patient-specific lock solution should be installed by a certified dialysis nurse.

See Appendix 1 for recommendations on flow rates and injection pressures for a large number of commercially available CVCs, HCs, PICCs, and TIVADs in The Netherlands.

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Guideline Module Validity and Maintenance

Module[1]	Responsible authors[2]	Authorisation Year	Next evaluation of validity of guideline	Frequency of evaluation of validity[3]	Who surveys the acutality of this guideline[4]	Relevant factors for changing recommendations[5]
Safe use of Central Venous Catheters,	NVvR	2019	2024	5 years	NVvR	New information on safety of Central

[1] Name of module
[2] Responsible authors (per module)
[3] Time frame: Once every 6 months, year , two years, five years, longer
[4] Responsible scientific society
[5] Variety of reasons: new drugs, new therapies, et cetera

Haemodialysis Catheters, Peripherally Inserted Central Catheters, and Totally Implantable Venous Access Devices for contrast administration using power injectors						Venous Catheters, Haemodialysis Catheters, Peripherally Inserted Central Catheters, and Totally Implantable Venous Access Devices for contrast administration using power injectors

Appendix to Module 9: Overview of catheters (See disclaimer)

Note: 1 PSI = 6,895 kPa and 1 kPa = 0,145 PSI.

Firm	Product name	Type	Power Injectable	Min Pressure	Max Pressure	Max Flow	Remarks
				PSI	PSI	ml/s	All powerinjectable products are marked as purple, on hubs/clamps flow rate is shown.
Becton Dickinson	PowerLine®	CVC (cuff) tunnelled CVC	Yes	N.A.	300	5 ml/s	5Fr SL/DL, 6 FR DL/TL
Becton Dickinson	PowerGlide Pro™	Midline	Yes	N.A.	300	7 ml/s	18 gauge is 7 ml max., 20-22 gauge is resp.5 and 2 ml max
Becton Dickinson	PowerMidline™	Midline	Yes	N.A.	300	7ml/sec	3Fr SL 3ml/sec, 4Fr SL 7ml/sec; 4Fr DL 4ml/sec, 5Fr DL 7ml/sec
Becton Dickinson	PowerPICC®	Peripherally inserted CVC	Yes	N.A.	300	5 ml/s	
Becton Dickinson	PowerPICC SOLO®	Peripherally inserted CVC	Yes	N.A.	300	5 ml/s	All Bard PICCs are available in nursing/IR and Full trays en met Sherlock 3CG technology 3Fr SL, 4Fr SL, 5Fr DL, 6FrTL
Becton Dickinson	PowerHickman®	CVC (cuff) tunnelled CVC	Yes	N.A.	300	5 ml/s	8Fr SL; 9,5Fr DL 5ml/sec
Becton Dickinson	Hickman®	CVC (cuff) tunnelled CVC	No	N.A.	25	NA	SL: 6,6Fr; 9,6Fr; DL:7,0Fr; 9Fr;12Fr; TL: 10Fr;12,5Fr
Becton Dickinson	Broviac®	CVC (cuff) tunnelled CVC	No	N.A.	25	NA	2,7Fr; 4,2Fr 6,6Fr
Becton Dickinson	PowerPort®	PAC (port catheter)	Yes	N.A.	300	5 ml/s	in combination with high pressure safety needle
Becton Dickinson	PowerPort® isp	PAC (port catheter)	Yes	N.A.	300	5ml/sec	in combination with high pressure safety needle
Becton Dickinson	PowerPort® SLIM	PAC (port catheter)	Yes	N.A.	300	5 ml/s	in combination with high pressure safety needle
Becton Dickinson	PowerPICC® Small Vessel	Peripherally inserted CVC	Yes	N.A.	300	1-2.5 ml/s	3 fr. Flow rate is 1 ml/sec at 300 psi, Double lumen 4 fr. Flow rate is 2.5 ml/sec at 300 psi.
Becton Dickinson	Niagara™	Acute dialysis catheter	No	N.A.			Straight and precurved 13,5Fr
Becton Dickinson	Niagara™ Slim	Acute dialysis catheter	No	N.A.			Straight and precurved 12Fr

Becton Dickinson	Power Trialysis®	Acute dialysis catheter	Yes	N.A.	300	5ml/sec	Straight and Alpha curved 13Fr
Becton Dickinson	Hickman® Dialyse	Chronic dialysis catheter (cuff)	No	N.A.		N.A.	Straight and Alphacurve® 14,5Fr en 16Fr
Becton Dickinson	HemoStar®	Chronic dialysis catheter (cuff)	No	N.A.		N.A.	Straight and Alphacurve® 14,5Fr en 16Fr
Becton Dickinson	HemoSplit®	Chronic dialysis catheter (cuff)	No	N.A.		N.A.	Straight and Alphacurve® 14,5Fr en 16Fr
Becton Dickinson	Equistream®	Chronic dialysis catheter (cuff)	No	N.A.		N.A.	Straight and Alphacurve® 14,5Fr en 16Fr
Becton Dickinson	GlidePath®	Chronic dialysis catheter (cuff)	No	N.A.		N.A.	Straight and Alphacurve® 14,5Fr
FMC	Pro-PICC catheter (with clamps)	Catheter only package	Yes	N.A.	300	5 ml/sec	All power injectable products are marked as purple
FMC	Pro-PICC catheter (with clamps)	Basic Set	Yes	N.A.	300	5 ml/sec	All power injectable products are marked as purple
FMC	Pro-PICC catheter (with clamps)	Long Wire Set	Yes	N.A.	300	5 ml/sec	All power injectable products are marked as purple
FMC	Pro-PICC catheter (with clamps)	Nursing Set (safety kit)	Yes	N.A.	300	5 ml/sec	All power injectable products are marked as purple
FMC	Valved PRO-PICC cath. (clamp free)	Catheter only package	Yes	N.A.	300	5 ml/sec	All power injectable products are marked as purple
FMC	Valved PRO-PICC cath. (clamp free)	Basic Set	Yes	N.A.	300	5 ml/sec	All power injectable products are marked as purple
FMC	Valved PRO-PICC cath. (clamp free)	Long Wire Set	Yes	N.A.	300	5 ml/sec	All power injectable products are marked as purple
FMC	Valved PRO-PICC cath. (clamp free)	Nursing Set (safety kit)	Yes	N.A.	300	5 ml/sec	All power injectable products are marked as purple
FMC	Midlines CT Rated SL	CT Rated	Yes	N.A.	300	5 ml/sec Single Lumen	All power injectable products are marked as purple
FMC	Midlines CT Rated DL	CT Rated	Yes	N.A.	300	7 ml/sec Double Lumen	All power injectable products are marked as purple
FMC	Pro-Fuse CT Poortkatheters	PAC standard	Yes	N.A.	300	5 ml/sec	All power injectable products are marked as purple
FMC	Pro-Fuse CT	PAC low profile	Yes	N.A.	300	5 ml/sec	All power injectable products are marked as purple

	Poortkatheters						
FMC	Pro-Fuse CT Poortkatheters	PAC Dual Dignity	Yes	N.A.	325	5 ml/sec	All power injectable products are marked as purple
FMC	Pro-Line Tunneled CVC	CVC tunneled	Yes	N.A.	300	5 ml/sec	All power injectable products are marked as purple
Smiths Medical	Port-a-Cath ® POWER PAC Standard (titanium or polysulfoon)	PAC	Yes	N.A.	300	5 ml/sec	All Power injectable ports are marked with a CT identifier, in combination with high pressure safety non-coring needle
Smiths Medical	Port-a-Cath ® POWER PAC Low Profile (titanium or polysulfoon)	PAC	Yes	N.A.	300	5 ml/sec	All Power injectable ports are marked with a CT identifier, in combination with high pressure safety non-coring needle
Smiths Medical	Port-a-Cath ® POWER PAC Dual lumen Low Profile	PAC	Yes	N.A.	300	5 ml/sec	All Power injectable ports are marked with a CT identifier, in combination with high pressure safety non-coring needle
Smiths Medical	P.A.S Port® T2 POWER PAC	PAC	Yes	N.A.	300	5 ml/sec	All Power injectable ports are marked with a CT identifier, in combination with high pressure safety non-coring needle
Smiths Medical	Gripper Plus® POWER PAC	Safety huber needle	Yes	N.A.	300	5 ml/sec	Distinctive blue extension line and 5 ml/sec markings on clamp for easy identification of capability for power injection
Smiths Medical	Gripper Plus® POWER PAC with needlefreee connector	Safety huber needle	Yes	N.A.	300	5 ml/sec	Distinctive blue extension line and 5 ml/sec markings on clamp for easy identification of capability for power injection
Smiths Medical	DeltaVen® Single port with end cap (24G - 16G)	Closed System / Integrated Safety Peripheral Catheter	Yes	N.A.	330	Please check table in attachment	
Smiths Medical	DeltaVen® Dual port with end caps (24G - 16G)	Closed System / Integrated Safety Peripheral Catheter	Yes	N.A.	330	Please check table in attachment	
Smiths Medical	DeltaVen® Stopcock (24G - 16G)	Closed System / Integrated Safety Peripheral Catheter	Yes	N.A.	330	Please check table in attachment	
Smiths Medical	DeltaVen® Dual port with needlefree connectors (24G - 16G)	Closed System / Integrated Safety Peripheral Catheter	Yes	N.A.	330	Please check table in attachment	

Smiths Medical	ProtectIV® Straight (FEP)	Safety Peripheral Catheter	Yes	N.A.	300		
Smiths Medical	ProtectIV® Straight (PUR)	Safety Peripheral Catheter	Yes	N.A.	300		
Smiths Medical	ProtectIV® Winged (FEP)	Safety Peripheral Catheter	Yes	N.A.	300		
Smiths Medical	ProtectIV® Winged (PUR)	Safety Peripheral Catheter	Yes	N.A.	300		
Smiths Medical	ViaValve™	Safety Peripheral Catheter	Yes	N.A.	300		
Baxter	GDK-1115	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GDK-1117,	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GDK-1120	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GDK-1125	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GDK-1112,	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GDK-1115J	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GDK-1117,	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GDK-1120J	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GDK-1215	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GDK-1220	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GDHK-1115	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GDHK-1117,	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GDHK-1120	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GDHK-1125	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GDHK-1115J	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GDHK-1117,	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GDHK-1120J	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GDHK-1315	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GDHK-1317,	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GDHK-1320	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GDHK-1325	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GDHK-1315J	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GDHK-1317,	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GDHK-1320J	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GTHK-1315	Basic kit	No	N.A.	N.A.	N.A	

Baxter	GTHK-1317,	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GTHK-1320	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GTHK-1325	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GTHK-1315J	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GTHK-1317,	Basic kit	No	N.A.	N.A.	N.A	
Baxter	GTHK-1320J	Basic kit	No	N.A.	N.A.	N.A	
Cook Medical	Turbo-Ject® Power-Injectable PICC	Over the wire set	Yes	N.A.	325	3, 5,or 7 ml/sec	purple marked lumen are power injectable. 4Fr single is max flow 5 ml/sec, 5Fr single lumen is max 7 ml/sec, 4Fr double 3 ml/sec, 5Fr double is 5ml/sec. 130cm wire included
Cook Medical	Turbo-Ject® Power-Injectable PICC	Bedside set	Yes	N.A.	325	3, 5,or 7 ml/sec	purple marked lumen are power injectable. 4Fr single is max flow 5 ml/sec, 5Fr single lumen is max 7 ml/sec, 4Fr double 3 ml/sec, 5Fr double is 5ml/sec.40cm wire included
Cook Medical	Turbo-Ject® Power-Injectable PICC	Standard set	Yes	N.A.	325	3, 5,or 7 ml/sec	purple marked lumen are power injectable. 4Fr single is max flow 5 ml/sec, 5Fr single lumen is max 7 ml/sec, 4Fr double 3 ml/sec, 5Fr double is 5ml/sec.60cm wire included
COOK Medical	Spectrum antibiotic impregnated CVC	CVC	No	N.A.	N.A.	Depends on size	2-lumen, 4,5 Fr, 5-15 cm
COOK Medical	Spectrum antibiotic impregnated CVC	CVC	No	N.A.	N.A.	Depends on size	3-lumen, 5,7 Fr, 5-25 cm
COOK Medical	Spectrum antibiotic impregnated CVC	CVC	No	N.A.	N.A.	Depends on size	5-lumen, 10 Fr, 15-25 cm
COOK Medical	Heparine bonded CVC	CVC	No	N.A.	N.A.	Depends on size	2-lumen, 4,5 Fr, 5-15 cm
COOK Medical	Heparine bonded CVC	CVC	No	N.A.	N.A.	Depends on size	3-lumen, 5,7 Fr, 5-25 cm
COOK Medical	CVC PUR	CVC	No	N.A.	N.A.	Depends on size	1-lumen, 3,4,5,6 Fr, 5-15 cm
COOK Medical	CVC PUR	CVC	No	N.A.	N.A.	Depends on size	2-lumen, 5,8 Fr, 5-25 cm
COOK Medical	CVC PUR	CVC	No	N.A.	N.A.	Depends on size	3-lumen, 5,7,9 Fr, 5-20 cm
COOK Medical	CVC PUR	CVC	No	N.A.	N.A.	Depends on size	5-lumen, 10 Fr, 15-25 cm
COOK Medical	UPICDS-4.0-CT-40NT-1110	Picclijn	Yes	N.A.	325 psi	3, 5,or 7 ml/sec	
COOK	UPICDS-4.0-CT-	Picclijn	Yes	N.A.	325 psi	3, 5,or 7	

Medical	40NT-1111					ml/sec	
COOK Medical	UPICDS-4.0-CT-NT-1110	Picclijn	Yes	N.A.	325 psi	3, 5,or 7 ml/sec	
COOK Medical	UPICDS-4.0-CT-NT-1111	Picclijn	Yes	N.A.	325 psi	3, 5,or 7 ml/sec	
COOK Medical	UPICDS-4.0-CT-OTW-ST-1111	Picclijn	Yes	N.A.	325 psi	3, 5,or 7 ml/sec	
COOK Medical	UPICDS-5.0-CT-40NT-1111	Picclijn	Yes	N.A.	325 psi	3, 5,or 7 ml/sec	
COOK Medical	UPICDS-5.0-CT-NT-1110	Picclijn	Yes	N.A.	325 psi	3, 5,or 7 ml/sec	
COOK Medical	UPICDS-5.0-CT-NT-1111	Picclijn	Yes	N.A.	325 psi	3, 5,or 7 ml/sec	
COOK Medical	UPICDS-5.0-CT-OTW-ST-1110	Picclijn	Yes	N.A.	325 psi	3, 5,or 7 ml/sec	
COOK Medical	UPICDS-5.0-CT-OTW-ST-1111	Picclijn	Yes	N.A.	325 psi	3, 5,or 7 ml/sec	
COOK Medical	UPICDS-501-MPIS-NT	Picclijn	No	N.A.	N.A.	3, 5,or 7 ml/sec	
COOK Medical	UPICS-3.0-CT-40NT-1110	Picclijn	Yes	N.A.	325 psi	3, 5,or 7 ml/sec	
COOK Medical	UPICS-3.0-CT-NT-1110	Picclijn	Yes	N.A.	325 psi	3, 5,or 7 ml/sec	
COOK Medical	UPICS-4.0-CT-40NT-1110	Picclijn	Yes	N.A.	325 psi	3, 5,or 7 ml/sec	
COOK Medical	UPICS-4.0-CT-40NT-1111	Picclijn	yes	N.A.	325 psi	3, 5,or 7 ml/sec	
COOK Medical	UPICS-4.0-CT-NT-1110	Picclijn	Yes	N.A.	325 psi	3, 5,or 7 ml/sec	
COOK Medical	UPICS-4.0-CT-NT-1111	Picclijn	Yes	N.A.	325 psi	3, 5,or 7 ml/sec	
COOK Medical	UPICS-4.0-CT-OTW-ST-1110	Picclijn	Yes	N.A.	325 psi	3, 5,or 7 ml/sec	
COOK Medical	UPICS-4.0-CT-OTW-ST-1111	Picclijn	Yes	N.A.	325 psi	3, 5,or 7 ml/sec	
COOK	UPICS-401-MPIS	Picclijn	Yes	N.A.	N/A	3, 5,or 7	

Medical						ml/sec	
COOK Medical	UPICS-401-MPIS-NT	Picclijn	Yes	N.A.	N/A	3, 5,or 7 ml/sec	
COOK Medical	UPICS-5.0-CT-40NT-1111	Picclijn	Yes	N.A.	325 psi	3, 5,or 7 ml/sec	
COOK Medical	UPICS-5.0-CT-NT-1110	Picclijn	Yes	N.A.	325 psi	3, 5,or 7 ml/sec	
COOK Medical	UPICS-5.0-CT-NT-1111	Picclijn	Yes	N.A.	325 psi	3, 5,or 7 ml/sec	
COOK Medical	UPICS-5.0-CT-OTW-ST-1110	Picclijn	Yes	N.A.	325 psi	3, 5,or 7 ml/sec	
COOK Medical	UPICS-5.0-CT-OTW-ST-1111	Picclijn	Yes	N.A.	325 psi	3, 5,or 7 ml/sec	
COOK Medical	UPICS-501-MPIS	Picclijn	No	N.A.	N/A	3, 5,or 7 ml/sec	
COOK Medical	UPICS-501-MPIS-NT	Picclijn	No	N.A.	N/A	3, 5,or 7 ml/sec	
COOK Medical	UPICTS-6.0-CT-40NT-1110	Picclijn	Yes	N.A.	325 psi	3, 5,or 7 ml/sec	
COOK Medical	UPICTS-6.0-CT-NT-1110	Picclijn	Yes	N.A.	325 psi	3, 5,or 7 ml/sec	
COOK Medical	UPICTS-6.0-CT-OTW-ST-1110	Picclijn	Yes	N.A.	325 psi	3, 5,or 7 ml/sec	
Teleflex Medical	Arrow PICC 1 lumen Basic Nursing Kit	Basic Nursing Kit	Yes	N.A.	300	4 ml/s	Is 4 Fr and in 40, 50 en 55 cm
Teleflex Medical	Arrow PICC 2 lumen Basic Nursing Kit	Basic Nursing Kit	Yes	N.A.	300	4 ml/s	Is 5 Fr and in 40, 50 en 55 cm
Teleflex Medical	Arrow PICC 3 lumen Basic Nursing Kit	Basic Nursing Kit	Yes	N.A.	300	6 ml/s	Is 6 Fr and in 40, 50 en 55 cm
Teleflex Medical	Arrow PICC 1 lumen Interventional Radiology Kit	Interventional Radiology Kit	Yes	N.A.	300	4 ml/s	Is 4 Fr and in 40, 50 en 55 cm
Teleflex Medical	Arrow PICC 2 lumen Interventional Radiology Kit	Interventional Radiology Kit	Yes	N.A.	300	4 ml/s	Is 5 Fr and in 40, 50 and 55 cm

Teleflex Medical	Arrowg+ard Blue Advance™ PICC, 1 lumen	Basic Set of Maximal Barrier kit	Yes	N.A.	300	5 ml/s	Is 4,5 Fr and in 40, 50 and 55 cm
Teleflex Medical	Arrowg+ard Blue Advance™ PICC, 2 lumen	Basic Set of Maximal Barrier kit	Yes	N.A.	300	5 ml/s	Is 5,5 Fr and in 40, 50 and n 55 cm
Teleflex Medical	Arrowg+ard Blue Advance™ PICC, 3 lumen	Basic Set of Maximal Barrier kit	Yes	N.A.	300	6 ml/s	Is 6 Fr and in 40, 50 and n 55 cm
Teleflex Medical	Arrow Midline	Midline	No				1 lumen and n in 3, 4 and n 5 Fr
Teleflex Medical	Arrow High Pressure CVC's	CVC	Yes	N.A.	300/ 400	5 ml/s, 10ml/s	In 2, 3 and 4 lumen and in 16 cm and 20 cm lengh
Teleflex Medical	Arrow CVC's	CVC	No	N.A.	45	N/A	Very elaborate gamma of CVC's
Teleflex Medical	Arrow Acute dialyse 2 lumen	CVVH	No				In 12 and 14 Fr. In 16, 20 and 25 cm
Teleflex Medical	Arrow Acute dialyse 3 lumen	CVVH	No				In 12 Fr. In 16, 20 and 25 cm
B.Braun Medical	Celsite® Epoxy	PAC	Yes	N.A.	325	Depends of the diameter of the needle	All venous Celsite® Access Ports with titanium chamber are pressure resistant up to 325 PSI (Except Celsite® Valved)
B.Braun Medical	Celsite® ECG	PAC	Yes	N.A.	325	Depends of the diameter of the needle	All venous Celsite® Access Ports with titanium chamber are pressure resistant up to 325 PSI (Except Celsite® Valved)
B.Braun Medical	Celsite® Discreet	PAC	Yes	N.A.	325	Depends of the diameter of the needle	All venous Celsite® Access Ports with titanium chamber are pressure resistant up to 325 PSI (Except Celsite® Valved)
B.Braun Medical	Celsite® PSU	PAC	Yes	N.A.	325	Depends of the diameter of the needle	All venous Celsite® Access Ports with titanium chamber are pressure resistant up to 325 PSI (Except Celsite® Valved)
B.Braun Medical	Celsite® Concept	PAC	Yes	N.A.	325	Depends of the diameter of the needle	All venous Celsite® Access Ports with titanium chamber are pressure resistant up to 325 PSI (Except Celsite® Valved)
B.Braun Medical	Celsite® Double Port	PAC	Yes	N.A.	325	Depends of the diameter of the needle	All venous Celsite® Access Ports with titanium chamber are pressure resistant up to 325 PSI (Except Celsite® Valved)

B.Braun Medical	Celsite® PICC-Cel	PICC-line	Yes	N.A.	300	5 ml/sec	
B.Braun Medical	Certofix® Mono	CVC enkel lumen	No	N.A.	45	N.A.	
B.Braun Medical	Certofix® Duo	CVC dubbel lumen	No	N.A.	45	N.A.	
B.Braun Medical	Certofix® Trio	CVC drie lumen	No	N.A.	45	N.A.	
B.Braun Medical	Certofix® Quatro	CVC vier lumen	No	N.A.	45	N.A.	
B.Braun Medical	Certofix® Quinto	CVC vijf lumen	No	N.A.	45	N.A.	
Vygon	Lifecath PICC	PICC	No	–	21,75 psi	–	
Vygon	Lifecath CT-PICC Easy	PICC	Yes	–	325 psi	Up to 6 ml/s (Depending on diameter)	
Vygon	Maxflo Expert	PICC	Yes	–	325 psi	Up to 7 ml/s (Depending on diameter)	
Vygon	Lifecath Midline	Midline	No	–	21,75 psi	–	
Vygon	SmartMidline	Midline	Yes	–	2Fr: 150psi 3Fr: 100psi 4Fr: 300psi 5Fr: 325 psi	Up to 7 ml/s (Depending on diameter)	
Vygon	Polysite	Implantable ports	Yes	–	325 psi	Up to 5 ml/s (Depending on diameter)	
Vygon	Seesite	Implantable ports	Yes	–	300 psi	Up to 5 ml/s (Depending on diameter)	
Vygon	Sitimplant	Implantable ports	Yes	–	Catheter < 6,6F : 45psi Catheter ≥ 6,6F : 350 psi	Up to 7 ml/s (Depending on diameter)	
Vygon	Heliosite	Implantable ports	Yes	–	Catheter < 6,6F : 45psi	Up to 5 ml/s (Depending	

					Catheter ≥ 6,6F : 350 psi	on diameter)	
Vygon	Mini-Sitimplant	Implantable ports	No	–	45 psi	–	
Vygon	Nutricath S	Tunneled catheter	No	–	45 psi	–	
Vygon	Nutricath tunnel with cuff	Tunneled catheter	No	–	45 psi	–	
Vygon	Leadercuff	Tunneled catheter	No	–	45 psi	–	
Vygon	Lifecath™	Tunneled catheter	No	–	21,75 psi	–	
Vygon	Dialykit	Hemodialysis catheters	No	–	45 psi	–	
Vygon	Lifecath™ twin	Hemodialysis catheters	No	–	21,75 psi	–	
Vygon	Leaderflex	CVC 1 lumen	No	–	21,75 psi	–	
Vygon	Seldipur	CVC 1 lumen	No	–	21,75 psi	–	
Vygon	Leadercath	CVC 1 lumen	No	–	21,75 psi	–	
Vygon	Multicath < 7.5Fr	CVC 2 - 3 lumen	No	–	21,75 psi	–	
Vygon	Multicath ≥ 7.5Fr	CVC 2 - 3 - 4 - 5 - 7 lumen	Yes	–	150 psi	–	
Vygon	Multicath Expert ≥ 7.5Fr	CVC 2 - 3 - 4 - 5 - 7 lumen - Silver impregnated catheter	Yes	–	150 psi	–	
Vygon	Multistar < 7.5 Fr	CVC 2 - 3 lumen - Antibiotic (Rifampicin & Miconazole) impregnated catheter	No	–	21.75 psi	–	
Vygon	Multistar ≥ 7.5 Fr	CVC 2 - 3 - 4 - 5 -7 lumen - Antibiotic (Rifampicin & Miconazole) impregnated catheter	Yes	–	150 psi	–	

Disclaimer:
This overview is made with great care for detail. However this overview does not replace the responsibility of the user to check with the latest recommendations with the catheter manufacturer(s). This overview will not be updated until a full review of this guideline will be performed.

Module 10: Optimal treatment of contrast medium extravasation

Research question

What is the optimal treatment in contrast media extravasation?

Introduction

Extravasation of intravascular (intravenous or intra-arterial) injected contrast (hand or power injection) is a well-recognized complication of contrast enhanced imaging studies (CT and MRI and US), angiography and interventions. Currently the clinical consequences and most optimal management is a matter of debate.

Search and select criteria

To answer our clinical question a systematic literature analysis was performed.

P (Patient):	patients with extravasation after intravascular contrast Administration;
I (Intervention):	cContrast aspiration, cooling of area of contrast extravasation, fasciotomy, necrotectomie, dilution, flushing with sterile water, application of ice, anti-inflammatory agents, corticosteroid, removal catheter, elevation of the affected limb / extremity, cold compresses, Plastic Surgery Review, monitoring the patient, surgical consultation;
C (Comparison):	conservative treatment or comparison of interventions above;
O (Outcomes):	rhabdomyolysis, tissue necrosis, long term injury / disability, compartment syndrome, pain, swelling and ulceration.

Relevant outcome measures

The working group considered compartment syndrome, tissue necrosis, and permanent or long-term injury or disability critical outcome measures for the decision making process, and location and volume of extravasation, pain, swelling, ulceration important outcomes for the decision making process.

Methods

The databases Medline (OVID), Embase and the Cochrane Library were searched from 1st of January 1996 to 7th of February 2018 using relevant search terms for systematic reviews (SRs), randomized controlled trials (RCTs) and observational studies (OBS).

The literature search procured 480 hits: 1 SR, 41 RCTs and 438 OBS. Based on title and abstract a total of 22 studies were selected. After examination of full text a total of all studies were excluded and 0 studies definitely included in the literature summary.

Summary literature

Not applicable. There were no studies investigating the research question.

Conclusions

Not applicable. There were no studies investigating the research question.

Considerations

The working group has based this protocol on expert opinions and international guidelines.
At the end of the recommendations suggestions for further reading are given.

Extravasations and injuries

One or more of the following signs or symptoms can develop: progressive swelling or pain, altered tissue perfusion as evidenced by decreased capillary refill at any time after the extravasation has occurred, change in sensation in the affected limb, and skin ulceration or blistering. It is important to note that initial symptoms of a compartment syndrome may be relatively mild (such as limited to the development of focal paraesthesia).

Most extravasations result in minimal swelling or erythema, with no long-term sequelae.
Few extravasations result in significant tissue damage, i.e. severe skin necrosis and ulceration.
Compartment syndrome may be seen associated with extravasation of large volumes and after extravasation of relatively small volumes in less capacious areas.
Extravasation can occur during hand or power injection.

The risk of extravasation is much less with GBCA injections.

Risk factors

Location of extravasation:
Less capacious areas (such as over the ventral or dorsal surfaces of the wrist) – higher risk
More capacious areas (such as upper arm) – lower risk

Volume of extravasation:
Large volume of contrast medium – higher risk

Inability to communicate:
Infants, young children, and unconscious and debilitated patients

Management

- Recognition of the extravasation, stop infusion of contrast media immediately.
- Try to aspirate the extravasated contrast medium through the inserted needle.
- Mark off affected area.
- Consultation of a radiologist.
- Surgical consultation (plastic surgeon) should be obtained whenever there is concern for a severe injury. Alternative: consultation of a physician in the emergency department.
- Clear instructions should be given to the patient to be aware of alarming symptoms.
- Appropriate patient information leaflets should be available. One should consider having these available in multiple languages.
- Appointments for follow up, if necessary.
- The referring physician should be notified.
- Record contrast extravasation and treatment in patient record (name, volume, concentration, area, clinical findings).
- Record names of all professionals involved in the patient management in patient record.
- Report contrast extravasation as a complication in the local reporting system.

Treatment

Non-severe extravasation injury:

- Use of cold of warm compresses, helpful for relieving pain at the injection site.
- Use of cold compresses, mainly helpful for relieving pain at the injection site.
- Use of warm compresses, helpful in improving absorption of the extravasation as well as in improving blood flow, particularly distal to the site.
- Use of pain medication (analgesics).

- Elevation of the affected extremity above the level of the heart to decrease capillary hydrostatic pressure and thereby promote resorption of extravasated fluid is recommended.
- Clear instructions should be given to the patient to seek additional medical care, should there be any worsening of symptoms, skin ulceration, or the development of any neurologic or circulatory symptoms, including paraesthesias.

Severe extravasation injury:

- Surgical consultation (plastic surgeon).
- Clear instructions should be given to the patient about the follow-up.

Recommendations

Consider the following treatment options for contrast extravasation:
- Try to aspirate the extravasated contrast medium through an inserted needle.
- Mark affected area.
- Use compresses, for relieving pain at the injection site.
- Use painkillers.
- Elevate the affected extremity above the level of the heart.

Record contrast extravasation and treatment in the patient record (volume, concentration, area, clinical findings).

Give the patient clear instructions when to seek additional medical care:
- Any worsening of symptoms.
- Skin ulceration.
- Development of any neurologic or circulatory symptoms, including paraesthesia's.
- Give the patient a patient information leaflet.

For severe extravasation injury:
- Consult a plastic surgeon.
- Notify the referring physician.

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Guideline Module Validity and Maintenance

Module[1]	Responsible authors[2]	Authorisation Year	Next evaluation of validity of guideline	Frequency of evaluation of validity[3]	Who surveys the acutality of this guideline[4]	Relevant factors for changing recommendations[5]
Contrast extravasation	NVvR	2019	2024	5 years	NVvR	New information on treatment of contrast extravasation

[1] Name of module
[2] Responsible authors (per module)
[3] Time frame: Once every 6 months, year , two years, five years, longer
[4] Responsible scientific society
[5] Variety of reasons: new drugs, new therapies, et cetera

Module 11 Organisation of Health Care

Hospital-based protocols
Develop hospital-based protocols on the safe use of contrast media (CM) describing (preventive) measures, workflow and responsibilities. Protocols should be available about The prevention of adverse reactions.

Treatment of adverse reactions.
Safety of gadolinium use.
Contrast media extravasation.
Safe use of catheters using power injectors.

A panel of various local experts should establish these protocols. The panel members will depend on the specific protocol (including a nephrologist, a (plastic) surgeon, an internal medicine specialist, a pharmacologist, a cardiologist, an allergology specialist and a radiologist). The referring physician is held responsible for analysing and giving notice of the patient's kidney function and hypersensitivity reactions to contrast media, instructing about the patient's medication, and the patient's after-care. And for taking blood samples for laboratory testing (tryptase levels) in case of moderate to severe hypersensitivity reactions to contrast media and for referring the patient to an allergy specialist in case of moderate to severe hypersensitivity reactions to contrast media. The physician responsible for the procedure should take the decision about contrast administration. Make agreements with the allergy specialist about the procedure for referral and testing for contrast media allergy.
Actions can be delegated to others according to local rules and protocols.

Hypersensitivity reactions to contrast media and prevention
Have a description of preventive measures in patients with a previous allergic reaction, for outpatient and clinical patients. Appropriate patient information leaflets should be available, about the procedure and about the preventive measures. Including the instruction about not driving a car/motorcycle for 24 hours after administration of clemastine.

Workflow and responsibilities

Responsible person	Action and responsibility
Referring physician	Order procedure: contrast-enhanced CT, contrast-enhanced MRI or angiography / intervention Inform patient about procedure Assessment hypersensitivity reactions to contrast media Mention previous hypersensitivity reactions in the order Instruct patient about preventive measures Record severe hypersensitivity reactions to contrast media in allergy registry of the patient record Record all severe drug (including contrast media) adverse reactions at the National Pharmacovigilance Institute LAREB
Physician responsible for the procedure - Cardiologist/Radiologist/ Nuclear Medicine/ Radiotherapist	Check the order for the imaging examination/procedure Check previous hypersensitivity reactions to contrast media Determine examination protocol and the choice of intravascular contrast medium Determine prophylactic medication If there is disagreement about the examination order, consult the referring physician

	Order contrast medium and prophylaxis medication in patient record Record and authorize CM safety alerts in patient record Record all severe drug (including contrast media) adverse reactions at the National Pharmacovigilance Institute LAREB
Physician responsible for the procedure	Before and during examination/procedure: Check hypersensitivity reactions and prophylactic medication Check medication and contra-indications Administration of prophylactic medication Administration of contrast medium Recording prophylactic medication and contrast administration in patient record (name, concentration, volume) Recording presence of any hypersensitivity symptoms

Treatment of acute hypersensitivity reactions to contrast media

Have a description of measures in patients with an acute hypersensitivity reaction. Appropriate patient information leaflets should be available, including the instruction about not driving a car/motorcycle for 24 hours after administration of clemastine.

Workflow and responsibilities

Responsible person	Action and responsibility
Management of department of the Physician responsible for the procedure - Cardiologist/Radiologist/Nuclear Medicine/ Radiotherapist	Drugs (minimum requirement), equipment and protocol available in every room where contrast media are administered Crash cart in every department where CM are administered Telephone number rapid response team available Organisation of regular training of personnel dealing with contrast media in the management of hypersensitivity reactions to contrast media and other emergency situations.
Physician responsible for the procedure - Cardiologist/Radiologist/Nuclear Medicine/ Radiotherapist	Check and stabilize patient Stop infusing contrast media Act according to type of reaction If applicable, call rapid response team Keep patient for at least 30 minutes after contrast agent injection in a medical environment After administration of clemastine, instruct the patient that is not possible/safe to drive a car/motorcycle for 24 hours Determine serum tryptase 1-2h after start of CM administration
Physician responsible for the procedure	Record contrast administration in patient record (name, concentration, volume) – see details below Record moderate and severe hypersensitivity reactions to contrast media in patient record (in allergy registry)
Referring physician	Take blood samples for laboratory testing (tryptase levels) in case of moderate to severe hypersensitivity reactions to contrast media

	Refer patient to allergy specialist in case of moderate to severe hypersensitivity reactions to contrast media AND elevated tryptase levels Record name contrast medium in consult order
Allergy specialist	Test contrast medium given to patient, which caused a hypersensitivity reaction, and alternative contrast media

Gadolinium Safety

Have a description of the safety of macrocyclic and linear gadolinium-based contrast agents (GBCA), nephrogenic systemic fibrosis (NSF), signs of gadolinium deposition, preventive measures and when to evaluate kidney function. Use always macrocyclic GBCA. For liver MRI the use of intravenous linear GBCA is allowed, because they are taken up in the liver and meet an important diagnostic need. For MR arthrography the use of intra-articular linear GBCA is also allowed.

Workflow and responsibilities

Responsible person	Action and responsibility
Referring physician	Order procedure: contrast-enhanced MRI Check laboratory results for eGFR value or determine eGFR If eGFR < 30 ml/min, be careful with gadolinium-based contrast agents
Physician responsible for the procedure - Radiologist	Check order procedure Check eGFR if available If eGFR < 30 ml/min consider indication Re-examine the need for the use of contrast medium with respect to an unenhanced study or other potential imaging modalities If there is no agreement on indication consult referring physician
Physician responsible for the procedure - Radiologist	Before and during procedure: Check eGFR Check contra-indications Administration of contrast agent Recording contrast agent administration in patient record (name, volume, concentration)

Contrast Media Extravasation

Have a description of measures in patients with extravasation of contrast media. Appropriate patient information leaflets should be available.

Workflow and responsibilities

Responsible person	Action and responsibility
Physician responsible for the procedure - Cardiologist/Radiologist/Nuclear Medicine/ Radiotherapist	Clinical assessment of CM extravasation Treatment of non-severe extravasation injury If severe injury, consider a surgical consultation (if needed a plastic surgeon) Clear instructions to the patient to be aware of alarming symptoms Record CM extravasation and treatment in patient record Record contrast extravasation as a complication in the local reporting system Notify the referring physician

Contrast injection via central catheters and ports using power injectors
Have a description of the use of various catheters and ports applicable in the hospital, where use of power injectors for contrast media is permitted.

Workflow and responsibilities

Responsible person	Action and responsibility
Management of department of the Physician responsible for the procedure - Cardiologist/Radiologist/Nuclear Medicine/ Radiotherapist	A (digital) protocol should be available in every room where contrast media are administered using power injectors

Exceptions:
Emergency patients/ procedures
In case of a major life-threatening medical condition, requiring rapid decision making including emergency imaging or intervention, determination of the eGFR and assessment of hypersensitivity reactions to contrast media can be postponed. If it is possible to wait a short time without harm to the patient, eGFR should be determined immediately. And assessment of hypersensitivity reactions should be done. When indicated, preventive measures should be taken before the administration of intravascular contrast medium.

Recording of hypersensitivity reactions to contrast media
Proper recording of any hypersensitivity reaction to CM is important, but the way of recording is not well standardized and often insufficient (Balfour, 2015; Deng, 2019).

It is mandatory that the physician responsible for the administration of the CM accurately records the following:

- The contrast agent name, dose (volume, concentration), and time of administration in the imaging report and in the electronic patient file.
- The patient symptoms (blood pressure, pulse, respiration rate, oxygen saturation, skin abnormalities), the treatment given, and the response of the patient to the treatment in the imaging report and in the electronic patient file.
- Any clinical follow-up and advice on need for future premedication in the imaging report and in the electronic patient file.
- Any results of consultation with a drug allergy specialist on future CM administration in the electronic patient file.
- All details of the reaction (blood pressure, pulse, respiration rate, oxygen saturation, skin abnormalities, tryptase levels 1 to 2 hours after start of reaction), in the hospital adverse events register (“complicatie registratie”).
- The presence of a documented allergy in the electronic patient file allergy registry (“allergie registratie”). This reporting should be based on the name of contrast medium.

If the adverse reaction to a contrast medium is severe or unusual, report all details of the reaction to the National Pharmacovigilance Authority (LAREB).

Patient information leaflets

Appropriate patient information leaflets on the various radiological examinations with contrast medium should be available. The occurrence of late reactions must be mentioned in these leaflets. And indicate what patient should do, ask for advice at the hospital or consult their general practitioner.

In addition, appropriate patient information leaflets about preventive measures in patients with a previous allergic reaction, about treatment of acute hypersensitivity reactions to contrast media, and contrast extravasation should be available.

One should consider having these leaflets available in multiple languages.

Training of Personnel

It is important that personnel that work in departments where CM are administered to patients are regularly trained in the management of hypersensitivity reactions and other emergency situations. It has been shown that high-fidelity hands-on simulation training programs are more effective than other forms of training, such as didactic lectures or computer-base training (Wang, 2011; Wang, 2014; Parsian, 2018; Ali, 2019). Checklists and visual aids can help personnel in accurate management of hypersensitivity reactions to CM (Gardner, 2018; Parsian, 2018).

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