

## **Summary of recommendations**

### **1. Introduction/start page**

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### **2. PC-AKI**

#### **2.1 Definitions, terminology and clinical course**

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#### **2.2 Risk stratification and stratification tools**

##### **Clinical question**

How to identify patients at high risk for post-contrast acute kidney injury (PC-AKI) who receive intravascular iodine-containing contrast medium?

##### **Subquestions**

- 1) What is the risk for PC-AKI in patients receiving iodine-containing contrast administration compared to patients receiving no contrast administration?
- 2) Which risk factors for PC-AKI can be identified in patients scheduled for an imaging procedure with iodine-containing CM?
- 3) How should a history of kidney transplantation be taken into account when assessing a patient for PC-AKI risk?
- 4) How should a solitary kidney be taken into account when assessing a patient for PC-AKI risk?
- 5) How should the osmolality of iodine-containing contrast medium be taken into account when assessing PC-AKI risk?
- 6) How to use questionnaires and prediction tools to estimate risk of PC-AKI?

##### **Recommendations**

Optimal nephrology care should be the primary goal in all chronic kidney disease patients, especially with attention to hydration status and medication use.

Consider an alternative imaging technique that does not require iodine-containing CM in all patients with an increased risk of PC-AKI.

Consult a nephrologist/internist for patients with an eGFR <30 ml/min/1.73m<sup>2</sup>.

Aim for clinical euvoolemia, using normal saline or Ringer's lactate, before administration of intravascular iodine-containing CM, regardless of eGFR.

For patients undergoing intravascular administration of iodine-containing CM:  
Consider patients with an eGFR <30 ml/min/1.73m<sup>2</sup> at risk for PC-AKI.

Apply the same recommendations, indicated for patients with bilateral kidneys, to patients with a solitary kidney or kidney transplantation subjected to iodine-containing contrast administration.

Consider that low osmolar contrast media and iso-osmolar contrast media have the same renal safety profile.

Do not use prediction models or tools to estimate the risk of PC-AKI, since their validity and effect on clinical outcome is unclear.

## 2.3 Evaluation of eGFR

### Clinical question

How to assess kidney function before and after iodine-containing contrast administration?

#### Subquestions

- 1) What is the best way to assess renal function?
- 2) When should an eGFR calculation be performed prior to contrast administration?
- 3) When should an eGFR calculation be performed after contrast administration?
- 4) If PC-AKI is diagnosed, how should the patient be followed-up?
- 5) How long are eGFR calculations valid?

### Recommendations

#### *Physicians/clinicians*

Determine eGFR in each patient scheduled for Computed Tomography or Angiography with or without intervention with use of intravascular iodine-containing contrast media prior to CM administration.

The measurement of eGFR is valid for:

- maximally 7 days when the patient has an acute disease or an acute deterioration of a chronic disease;
- maximally 3 months when the patient has a known chronic disease with stable renal function;
- approx. 12 months in all other patients

Determine eGFR within 2 to 7 days after intravascular contrast administration in every patient for whom preventive measures against PC-AKI were taken.

If PC-AKI is diagnosed (by KDIGO criteria), follow the patient for at least 30 days post-diagnosis and re-assess serum creatinine.

#### *Laboratory specialists*

Measure the serum or plasma creatinine using a selective (enzymatic) method.

Implement the creatinine based CKD-EPI formula for estimation of the eGFR.

Consider correcting the eGFR for BSA in the CKD-EPI formula in case that the patient's specific body surface area (BSA) is known.

## 2.4 Prevention of PC-AKI

### 2.4.1 Hydration and complications

#### Clinical question

What hydration strategy should be recommended for patients undergoing radiological or cardiological examinations with intravascular iodine-containing contrast media?

Several subquestions arise when it comes to this particular subject:

- 1) Is there a significant difference in the incidence of PC-AKI comparing hydration versus no hydration?
- 2) Is there a significant difference in the incidence of PC-AKI comparing oral versus intra-venous pre- and post-hydration?
- 3) Is there a significant difference in the incidence of PC-AKI comparing intra-venous NaCl versus NaHCO<sub>3</sub>?
- 4) Is there a significant difference in the incidence of PC-AKI comparing intravenous pre-hydration versus pre- and post-hydration?
- 5) Is there a significant difference in the incidence of PC-AKI in patients undergoing controlled diuresis versus standard hydration schedules?

### Recommendations

For patients with an eGFR <30 ml/min/1,73m<sup>2</sup> undergoing intravascular administration of iodine-containing contrast medium either one of the following options can be used:

- prehydrate with 3ml/kg/h (or 250ml in total) NaHCO<sub>3</sub> 1.4% for 1h pre-CM administration;
- pre- and posthydrate with 3ml/kg/h (or 250ml in total) NaHCO<sub>3</sub> 1.4% for 1h pre-CM and 1ml/kg/h (or 500ml in total) for 6h post-CM administration.

Do not use hydration with controlled diuresis for the prevention of PC-AKI in patients undergoing (cardiac) angiography with or without intervention, unless it is performed in a research setting.

Do not use oral hydration as the sole means of prevention of PC-AKI.

### 2.4.2 Statins and hydration against PC-AKI

#### Clinical question

Should statins in addition to hydration be recommended to reduce the incidence of PC-AKI in patients with pre-existent reduced kidney function receiving intravascular contrast medium?

### Recommendations

Consider giving short term (48 hours) high dose atorvastatin or rosuvastatin in addition to hydration in statin-naïve patients with eGFR <60 ml/min/1.73m<sup>2</sup> undergoing coronary angiography with or without percutaneous coronary intervention.

### 2.4.3 Prophylactic NAC and hydration against PC-AKI

#### Clinical question

Should prophylactic N-acetylcysteine (NAC) in addition to hydration be recommended to reduce the incidence of PC-AKI in patients receiving intravascular iodine-containing contrast medium?

### Recommendations

Do not use NAC for the prevention of PC-AKI in patients with a normal or impaired (eGFR <60 ml/min/1,73m<sup>2</sup>) kidney function.

### 2.4.4 Vitamin C and hydration against PC-AKI

### **Clinical question**

Should prophylactic vitamin C in addition to hydration be recommended to reduce the incidence of PC-AKI in patients with pre-existent reduced kidney function receiving iodine-containing intravascular contrast medium?

### **Recommendations**

Do not use vitamin C exclusively for the prevention of Post Contrast Acute Kidney Injury (PC-AKI) in patients with a normal or impaired (eGFR <60 ml/min/1,73m<sup>2</sup>) kidney function.

## **2.4.5 Nephrotoxic medication and PC-AKI**

### **Clinical question**

Should nephrotoxic medication be discontinued prior to intravascular contrast administration to reduce the risk of post-contrast acute kidney injury (PC-AKI)?

### **Recommendations**

Do not routinely withhold ACE-inhibitors, angiotensin II receptor blockers or diuretics prior to intravascular iodine-containing contrast administration.

Withhold NSAIDs prior to intravascular iodine-containing contrast medium administration.

The working group recommends nephrology consultation before administering iodine-containing contrast in patients with eGFR <30 ml/kg/1.73m<sup>2</sup> to individualize continuation or discontinuation of ACE inhibitors, angiotensin II receptor blockers, diuretics or nephrotoxic drugs and weigh this against the potential benefits and harm of the administration of iodine-containing CM.

## **2.4.6 Prophylactic renal replacement against PC-AKI**

### **Clinical question**

Should prophylactic renal replacement therapy be recommended to reduce the risk of PC-AKI in patients with CKD stage 4 to 5 receiving intravascular contrast medium?

### **Recommendations**

Do not use prophylactic dialysis in patients with chronic kidney disease stage 4 to 5 receiving intravascular iodine-containing contrast medium for coronary angiography with or without percutaneous intervention, to lower the risk of post contrast acute kidney injury.

Do not use prophylactic hemofiltration routinely in patients with chronic kidney disease stage 4 to 5 receiving intravascular iodine-containing contrast medium for coronary angiography with or without percutaneous intervention.

Do not change the schedule of chronic dialysis for the purpose of an iodine-containing contrast-enhanced imaging study (or in other words: the scheduling of an iodine-containing contrast-enhanced imaging study does not need to be adapted to the dialysis schedule of the patient).

## **2.4.7 Nephrotoxicity of GBCA**

### **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?

### 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<sup>2</sup>.

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<sup>2</sup>) 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.

## 3. Hypersensitivity reactions

### 3.1 Introduction to hypersensitivity reactions

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### 3.2 Definitions of adverse drug reactions

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### 3.3 Management of acute hypersensitivity reactions

#### Clinical question

What is the optimal treatment for acute hypersensitivity reactions to 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 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:**

##### Cardiac or respiratory arrest:

- Start CPR.
- Call the CPR team.

##### Anaphylactic reaction or stridor:

- 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.

## 3.4 Treatment of late reactions to CM

### 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 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.

## 3.5 Follow up strategies for hypersensitivity reactions to CM

### 3.5.1 In vitro tests in patients with hypersensitivity reactions to CM

### Clinical question

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

### Recommendations

Measure serum tryptase, preferably between 1-2 hours (range 15 minutes to 4 hours) from the start of all moderate to severe immediate hypersensitivity reactions to contrast media. This measurement serves as a baseline for further allergologic examinations.

\*See also flow charts

Basophil activation tests are reserved for selected patients with moderate to severe acute hypersensitivity reactions and are only available in specialized drug allergy centres.

For nonimmediate hypersensitivity reactions there are no meaningful in vitro diagnostic tests available in the Netherlands.

### 3.5.2 Diagnostic value of skin tests for hypersensitivity reactions after CM

#### Clinical question

What should be done in patients with a history of hypersensitivity reactions after contrast media administration to decrease the risk of developing a recurrent hypersensitivity reaction?

#### Recommendations

Refer the patient to a drug allergy specialist to perform skin tests for the suspected culprit and several commonly used alternatives, ideally within 6 months after the hypersensitivity reaction.

Refer the following patient groups:

- Moderate to severe immediate hypersensitivity reactions to a contrast medium
- Severe mucocutaneous non-immediate hypersensitivity reactions to a contrast medium
- Hypersensitivity reactions to two or more different contrast media (e.g., two different iodine- based contrast media or gadolinium agents, or an iodine-based contrast medium and a gadolinium-based contrast agent)
- All patients with breakthrough hypersensitivity reactions despite premedication with corticosteroids and/or H1-antihistamines

\*See also flow charts

Always specify the used contrast medium in the referral to the drug allergy specialist.

### 3.5.3 Risk factors for hypersensitivity reactions to CM

#### Clinical question

Which patients are at increased risk of developing hypersensitivity reactions after contrast media administration?

#### Recommendations

Only consider a previous hypersensitivity reaction after contrast media administration a relevant risk factor for developing a new hypersensitivity reaction.

\*See also flow charts

### 3.5.4 Prophylactic measures to avoid hypersensitivity reactions to CM

#### Clinical question

Which prophylactic measures should be taken in patients at increased risk of hypersensitivity reactions to contrast media?

This question contains the following patient categories:

- I Patients with previous immediate (acute) hypersensitivity reactions to iodine-based contrast media or gadolinium-based contrast agents

- II Patients with a previous breakthrough reaction to contrast media
- III Patients with previous hypersensitivity reactions to multiple contrast media
- IV Patients with previous nonimmediate (delayed) hypersensitivity reactions to iodine-based contrast media or gadolinium-based contrast agents

In addition, the following subjects were elaborated:

- V Cross-reactivity between contrast media
- VI Documentation of hypersensitivity reactions

### **Recommendations**

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

\*See also flow charts

### I Patients with previous immediate (acute) hypersensitivity reactions to iodine-based contrast media or gadolinium-based contrast agents

In patients with a (documented) history of a **mild immediate** hypersensitivity reaction to an iodine-based contrast medium or a gadolinium-based contrast agent:

- Treat these patients as any other patient because of the low risk of developing a moderate or severe reaction

\*See also flow charts

In patients with a (documented) history of a **moderate or severe** hypersensitivity reaction to iodine-based contrast media or gadolinium-based contrast agents

- Postpone imaging and refer the patient to a drug allergy specialist

If there is no time to refer the patient to a drug allergy specialist:

- Choose a different iodine-based contrast medium or gadolinium-based contrast agent if the culprit contrast medium is known\*
- Consider a test dose by first giving 10% of the total contrast dose and observing the patient for >15 minutes; particularly with severe reactions and/or unknown culprit
- Observe the patient ≥ 30 min with IV in place
- Be vigilant to react to a possible new hypersensitivity reaction

\*See also flow charts

### II Patients with a previous breakthrough reaction to contrast media

In patients with a breakthrough hypersensitivity reaction to iodine-based contrast media or gadolinium-based contrast agents, always refer to a drug allergy specialist for skin testing with a panel of different iodine-based contrast media or gadolinium-based contrast agents.

\*See also flow charts

### III Patients with previous hypersensitivity reactions to multiple contrast media

In patients with hypersensitivity reactions to multiple iodine-based or gadolinium-based contrast media (either two or more different iodine-based contrast media or gadolinium-based contrast agents or to an iodine-based contrast medium and a gadolinium-based

contrast agent) apply the same as above, but always refer the patient to a drug allergy specialist.

\*See also flow charts

#### IV Patients with previous nonimmediate (delayed) hypersensitivity reactions to iodine-based contrast media or gadolinium-based contrast agents

- Do **not** give iodine-based contrast media or gadolinium-based contrast agents to a patient with a previous (suspected) severe nonimmediate skin eruption with danger signs\*\*
- Refer the patient immediately to a drug allergy specialist.

\*See also flow charts

In patients with a history of a mild-moderate nonimmediate skin eruption without danger signs\*\*:

- Choose a different iodine-based contrast medium or gadolinium-based contrast agent if the culprit contrast medium is known\*
- Instruct the patient in case of a recurrent reaction to take pictures of the skin lesions and contact the radiology or cardiology department for feedback

\*See also flow charts

\* Consider cross-reactivity of contrast media (see Tables 7.4.1 and 7.4.2) and an increased risk

for NIHR with use of iso-osmolar ICM.

\*\* Danger signs: erosive and/or haemorrhagic lesions, blistering and skin disruption, mucosal involvement, extracutaneous organ involvement (high fever, abnormal liver / kidney values, lymphadenopathy)

#### V Cross-reactivity between contrast media

Cross-reactivity is most relevant in *allergic* hypersensitivity reactions. It occurs with a higher frequency among:

- Iodine-based contrast media with a N-(2,3 hydroxypropyl)-carbamoyl side chain
- Macroyclic gadolinium-based contrast agents

The drug allergy specialist determines through skin testing with a panel of different iodine-based contrast media and gadolinium-based contrast agents:

- The allergic nature of the hypersensitivity reaction
- Cross-reactivity between contrast media
- Suggestions for safe alternative contrast media

#### VI Documentation of hypersensitivity reactions

The physician responsible for the administration of the contrast medium should accurately document the hypersensitivity reaction in the imaging report.

The physician responsible for the administration of the contrast medium or the drug allergy specialist should accurately document the hypersensitivity reaction in the electronic patient dossier.

It is essential that reporting should be based on the name of the specific contrast medium and be done by *physicians* or *drug allergy specialists* with experience in the use of contrast media.

After all hypersensitivity reactions to contrast media, the following should be registered:

- The place, date, and time of CM administration - in the imaging report and in the electronic patient record.
- The specific contrast medium name and dose (volume, concentration) - in the imaging report and in the electronic patient record.
- The type of hypersensitivity reaction, immediate or non-immediate - in the imaging report and in the electronic patient record.
- All patient symptoms and vital signs (blood pressure, pulse, respiration rate, oxygen saturation) - in the imaging report and in the electronic patient record.
- The treatment given and the response of the patient to the treatment - in the imaging report and in the electronic patient record.
- Any clinical follow-up and advice on the need for future premedication - in the imaging report and in the electronic patient record.
- Any results of the consultation with a drug allergy specialist on future CM administration - in the electronic patient record.

The physician responsible for the administration of the contrast medium or the drug allergy specialist should accurately document severe or unusual hypersensitivity reactions to the National Pharmacovigilance Authority LAREB.

### 3.5.5 Hypersensitivity reactions after non-vascular CM

#### Clinical question

Which prophylactic measures should be taken in patients at increased risk of hypersensitivity reactions to nonvascular contrast media?

#### 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.

## 4. GBCA

### 4.1 Risk factors and prevention of NSF

#### 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<sup>2</sup>.

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 haemodialysis 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<sup>2</sup>) 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.

### 4.2 Gadolinium deposition

#### 4.2.1 Introduction to gadolinium deposition

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#### 4.2.2 Gadolinium deposition in the brain and body

#### Clinical question

What is the effect of gadolinium deposition in the brain and body?

#### Recommendations

To date, even though there is evidence that gadolinium is deposited in tissues, there is no evidence of clinical symptoms nor harm associated with gadolinium deposition in the brain and body.

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

\*See also module Strategies for Dose Reduction of Gadolinium-Based Contrast Agents

This guideline committee supports the ACR Committee on Drugs and Contrast Media's suggested terminology of Symptoms Associated with Gadolinium Exposure (SAGE) for self-reported symptoms and signs.

#### 4.2.3 Strategies for dose reduction of GBCA

##### Clinical question

In which way can the dose of gadolinium be reduced / minimized without compromising diagnostic accuracy?

The following categories were defined:

- I Potential dose-reduction strategies for neuroimaging with gadolinium-based contrast agents
- II Potential dose-reduction strategies for cardiovascular imaging with gadolinium-based contrast agents
- III Potential dose-reduction strategies for musculoskeletal imaging with gadolinium-based contrast agents
- IV Potential dose-reduction strategies for abdominal imaging with gadolinium-based contrast agents
- V Potential dose-reduction strategies for breast imaging with gadolinium-based contrast agents

##### Recommendations

###### I Potential dose-reduction strategies for neuroimaging with gadolinium-based contrast agents

Findings of the LEADER-75 trial indicate that the dose of gadolinium-based contrast agents (gadobutrol) may be reduced to up to 75% of the standard dose (0.075 mmol/kg bodyweight (equivalent to 0.075 ml/kg bodyweight)) in patients with suspected brain lesions.

The use of deep learning based methods for gadolinium dose reduction in patients suspected with brain metastasis is not recommended based on the current literature.

###### II Potential dose-reduction strategies for cardiovascular imaging with gadolinium-based contrast agents

The use of standard dose imaging is recommended in patients with clinical indications for the administration of gadolinium-based contrast agents in cardiac MRI.

Non-CE MRA techniques (e.g., time-of-flight MRA) and are widely available and can be used for accurate evaluation of stenosis grade of the supra-aortic vasculature.

Non-CE ECG-gated MRA sequences are widely available and recommended over (low-dose) CE MRA techniques for the evaluation of aortic dimensions.

###### III Potential dose-reduction strategies for musculoskeletal imaging with gadolinium-based contrast agents

The use of standard dose imaging is recommended in patients with clinical indications for the administration of gadolinium-based contrast agents in musculoskeletal imaging.

#### IV Potential dose-reduction strategies for abdominal imaging with gadolinium-based contrast agents

##### *Prostate*

There is increasing evidence that biparametric (T2w + DWI) protocols may be used as an alternative to multiparametric (T2w + DWI + DCE) protocols for the detection of prostate cancer.

##### *Liver*

The use of standard dose imaging is recommended in patients with clinical indications for the administration of gadolinium-based contrast agents in liver MRI.

#### V Potential dose-reduction strategies for breast imaging with gadolinium-based contrast agents

The use of standard dose imaging is recommended in patients with clinical indications for the administration of gadolinium based contrast agents in breast MRI.

### **4.2.4 GBCA 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?

#### **Recommendations**

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

## **5. Pregnancy and lactation**

### **5.1 Safe use of CM during pregnancy**

#### **Clinical question**

What is the safety profile of contrast media (iodine-based contrast media or gadolinium-based contrast agents) during pregnancy for mother and child?

#### **Recommendations**

Do not withhold a pregnant patient imaging with iodine-based contrast media when this is medically indicated.

Be cautious with gadolinium-based contrast agents due to potential risks to the foetus. Only use contrast agents when the benefits clearly outweigh the possible risks.

### **5.2 Safe use of CM during lactation**

#### **Clinical question**

What is the safety profile of contrast media (iodine-based contrast media or gadolinium-based contrast agents) during the lactation period for mother and child?

## **Recommendations**

Due to the limited amount of excretion of contrast media into breast milk, the guideline development group believes it is safe to continue breastfeeding after administration of contrast media.

If patients wish to discontinue breastfeeding (shared decision making), a discontinuation of 24 hours is sufficient.

## **6. Rare diseases**

### **6.1 Safe use of contrast media in patients with Multiple Myeloma**

#### **Clinical question**

Which prevention strategies are effective to prevent contrast-associated acute kidney injury (CA-AKI) in patients with Multiple Myeloma?

#### **Recommendations**

Always consider the general principles for prevention of acute kidney injury that were published in the guideline Safe Use of Contrast Media, Part 1:

- Optimal nephrology care should be the primary goal in all chronic kidney disease patients, with attention to hydration status and medication use.
- Aim for clinical euvoolemia, using normal saline or Ringer's lactate, before administration of intravascular iodine-based contrast media, regardless of eGFR.
- Consider patients with an eGFR <30 ml/min/1.73m<sup>2</sup> at risk for CA-AKI.
- Consult a nephrologist/internist for patients with an eGFR <30 ml/min/1.73m<sup>2</sup>.

Determine in each patient with multiple myeloma whether administration of iodine-based contrast media is indicated or if an alternative imaging technique is possible.

- Apply the same precautions to prevent contrast-associated acute kidney injury (CA-AKI) in patients with multiple myeloma as in subjects without this disease, if there are no additional risk factors associated with multiple myeloma for development of acute renal insufficiency.
- For (euvolemic) patients with an eGFR <30 ml/min/1,73m<sup>2</sup> undergoing intravascular administration of iodine-based contrast media prehydrate with 3ml/kg/h NaHCO<sub>3</sub> 1.4% for 1h (or a total of 250ml) pre-CM administration.

In selected patients with additional risk factors associated with multiple myeloma for development of acute renal insufficiency (e.g., hypercalcemia, light chain cast nephropathy, amyloidosis), close consultation between the haematologist and imaging physician is needed to ensure an optimal risk-benefit balance, including whether administration of contrast media is warranted and if preventive measures are needed.

### **6.2 Safe use of contrast media in patients with Pheochromocytoma or Paraganglioma**

#### **Clinical question**

What safety strategy should be used for contrast media administration in patients with pheochromocytoma or paraganglioma (PPGL)?

This clinical question includes the following underlying question:

- How should intra-arterial and intravenous contrast administration be applied in patients with pheochromocytoma or paraganglioma?

#### **Recommendations**

Prophylactic treatment with an  $\alpha$ -adrenergic receptor blocker ( $\pm \beta$ -adrenergic receptor blocker) is not indicated before intravenous administration of iodine-based contrast media in patients with pheochromocytoma or paraganglioma.

Prophylactic treatment with an  $\alpha$ -adrenergic receptor blocker ( $\pm \beta$ -adrenergic receptor blocker) is not indicated before intra-arterial administration of iodine-based contrast media in patients with pheochromocytoma or paraganglioma.

Gadolinium-based contrast agents and ultrasound contrast agents may be safely used in patients with pheochromocytoma or paraganglioma.

### **6.3 Safe use of contrast media in patients with Myasthenia Gravis**

#### **Clinical question**

What is role of contrast media in patients with exacerbations of myasthenia gravis after contrast media administration?

#### **Recommendations**

Do not withhold contrast media to patients with myasthenia gravis, as the risk of a contrast media induced myasthenic exacerbation is very low.

### **6.4 Safe use of contrast media in patients with Mastocytosis**

#### **Clinical question**

Which strategies are effective in preventing hypersensitivity reactions and anaphylactic shock in patients with systemic mastocytosis after contrast media administration?

#### **Recommendations**

Do not withhold iodine-based contrast media or gadolinium-based contrast agents in patients with systemic mastocytosis.

Recommendation for administration of contrast media in patients with systemic mastocytosis:

- Continue maintenance anti-allergic medication (e.g., H1-/H2-antihistamines)
- Be vigilant to react to a possible hypersensitivity reaction
- Observe the patient  $\geq 30$  min with IV in place
- In case of an allergic reaction, refer to a drug allergy specialist

## **7. DM**

### **7.1 Iodine-based CM and diabetes mellitus (DM)**

#### **Clinical question**

Should metformin be discontinued in patients undergoing intravascular contrast administration for radiological examination to prevent metformin-associated lactic acidosis (MALA)?

## **Recommendations**

Continue metformin in all patients with an eGFR  $\geq 30 \text{ ml/min}/1.73\text{m}^2$  scheduled for imaging to whom intravascular iodine-containing contrast medium is administrated.

Discontinue metformin in all patients with an eGFR  $< 30 \text{ ml/min}/1.73\text{m}^2$  to whom intravascular iodine-containing contrast medium is administrated as soon as this level of kidney dysfunction is detected and inform the requesting and prescribing physician.

## **8. CIE**

### **8.1 Prevention of contrast-induced encephalopathy (CIE)**

#### **Clinical question**

What are strategies for the prevention of iodine-induced thyroid dysfunction in:

- Patients with a history of cardiovascular disease and/or more than 65 years old
- Patients with a history of thyroid problems (goitre, hyperthyroidism, hypothyroidism)
- Patients who receive radioactive iodine treatment of the thyroid

#### **Recommendations**

Do not routinely measure the thyroid function before administration of iodine-based contrast media.

Consider measurement of thyroid function in high-risk patients for iodine-induced hyperthyroidism, especially in subjects older than 65 years and those with severe cardiovascular morbidity.

Consider prophylactic treatment prescribed by an internal medicine specialist in selected patients with subclinical hyperthyroidism receiving iodine-based contrast media (e.g., patients older than 65 years or with severe cardiovascular morbidity), starting one day before contrast administration and continuing for 14 days, consisting of thiamazole 30 mg once daily, with possible addition of potassium perchlorate 500 mg twice daily.

Avoid isotope imaging of the thyroid and/or radioactive iodine treatment for 4 to 8 weeks after iodine-based contrast media injection or withhold iodine-based contrast media administration 4 to 8 weeks before planned isotope imaging of the thyroid or radioactive iodine treatment.

## **9. IIHT**

### **9.1 Prevention of Iodine-Induced Hyperthyroidism (IIHT) after use of iodine-based CM**

#### **Clinical question**

Which strategies are effective for prevention of Contrast-Induced Encephalopathy (CIE)?

#### **Recommendations**

Health care providers should be aware of the existence of Contrast-Induced Encephalopathy (CIE) following iodine-based contrast media administration.

Adequate prevention strategies have not been investigated in detail. General advice for clinical practice:

1. Minimize the amount of iodine-based contrast media as much as possible during endovascular interventions.
2. Consider to hydrate patients with severe renal dysfunction (eGFR <30 ml/min/1.73m<sup>2</sup>) receiving iodine-based contrast media (see protocol in Safe Use of Contrast Media Part 1).
3. Closely monitor patients the first six hours after endovascular interventions for neurological symptoms and consult a neurologist immediately in case of neurological symptoms.
4. Depending on the clinical symptoms of contrast-induced encephalopathy, treatment with antiepileptic drugs, corticosteroids, intravenous hydration, and/or mannitol may be recommended.

## 10. Safe time intervals and analytical interference

### 10.1 Multiple investigations with contrast media in patients with normal or reduced kidney function

#### Clinical question

What is a safe time interval in patients with normal and reduced renal function between two radiological or cardiological examinations with contrast media?

What is a safe time interval in patients with reduced renal function between:

- 1 Two examinations using enhanced imaging with iodine-based contrast media?
- 2 Two examinations using enhanced imaging with gadolinium-based contrast agents?
- 3 Two examinations using enhanced imaging with an iodine-based contrast medium and a gadolinium-based contrast agent?

This question contains the following subgroups:

- Elective CT/Angio/MRI in patients with normal renal function (eGFR >60 ml/min/1.73m<sup>2</sup>)
- Elective CT/Angio/MRI in patients with moderately reduced renal function (eGFR 30-60 ml/min/1.73m<sup>2</sup>)
- Elective CT/Angio/MRI in patients with severely reduced renal function (eGFR < 30 ml/min/1.73m<sup>2</sup>)
- CT/Angio/MRI in emergency or life-threatening situations

#### Recommendations

##### 1. Safe time intervals in enhanced imaging with iodine-based contrast media

Consider a waiting time between **elective** contrast-enhanced CT or (coronary) angiography with successive iodine-based contrast media administrations in patients with **normal renal function** (eGFR >60 ml/min/1.73m<sup>2</sup>) of:

- Optimally 12 hours (near complete clearance of the previously administered iodine-based contrast media)
- Minimally 4 hours (if clinical indication requires rapid follow-up)

Consider a waiting time between **elective** contrast-enhanced CT or (coronary) angiography with successive iodine-based contrast media administrations in patients with **moderately reduced renal function** (eGFR 30-60 ml/min/1.73m<sup>2</sup>) of:

- Optimally 48 hours (near complete clearance of the previously administered iodine-based contrast media)
- Minimally 16 hours (if clinical indication requires rapid follow-up)

Consider a waiting time between **elective** contrast-enhanced CT or (coronary) angiography with successive iodine-based contrast media administrations in patients with **severely reduced renal function** (eGFR < 30 ml/min/1.73m<sup>2</sup>) of:

- Optimally 168 hours (near complete clearance of the previously administered iodine-based contrast media)
- Minimally 60 hours (if clinical indication requires rapid follow-up)

**In emergency or life-threatening situations**, employ less waiting time between contrast-enhanced CT or (coronary) angiography with successive iodine-based contrast media administrations.

## 2. Safe time intervals in enhanced imaging with gadolinium-based contrast agents

Consider a waiting time between **elective** contrast-enhanced MRI with successive gadolinium- based contrast agent administrations in patients with **normal renal function** (eGFR >60 ml/min/1.73m<sup>2</sup>) of:

- Optimally 12 hours (near complete clearance of the previously administered gadolinium- based contrast agent)
- Minimally 4 hours (if clinical indications require rapid follow-up)

Consider a waiting time between **elective** contrast-enhanced MRI with successive gadolinium- based contrast agent administrations in patients with **moderately reduced renal function** (eGFR 30-60 ml/min/1.73m<sup>2</sup>) of:

- Optimally 48 hours (near complete clearance of the previously administered gadolinium- based contrast agent)
- Minimally 16 hours (if clinical indications require rapid follow-up)

Consider a waiting time between **elective** contrast-enhanced MRI with successive gadolinium- based contrast agent administrations in patients with **severely reduced renal function** (eGFR < 30 ml/min/1.73m<sup>2</sup>) of:

- Optimally 168 hours (near complete clearance of the previously administered gadolinium- based contrast agent)
- Minimally 60 hours (if clinical indications require rapid follow-up)

**In emergency or life-threatening situations**, employ less waiting time between contrast-enhanced MRI with successive gadolinium-based contrast agent administrations.

## 3. Safe time intervals in enhanced imaging with an iodine-based contrast medium and a gadolinium- based contrast agent

When combining contrast-enhanced CT or (coronary) angiography with an iodine-based contrast medium and contrast-enhanced MRI with a gadolinium-based contrast agent on the same day in **elective** situations, it is better to start with the MRI examination, unless the CT examination is intended for the kidneys, ureters, or bladder (CT Urography).

Consider a waiting time between **elective** contrast-enhanced MRI with a gadolinium-based contrast agent and contrast-enhanced CT or (coronary) angiography with an iodine-based contrast medium in patients with **normal renal function** (eGFR >60 ml/min/1.73m<sup>2</sup>) of:

- Optimally 6 hours (near complete clearance of the effects of the previously administered gadolinium-based contrast agent)
- Minimally 2 hours (if the clinical indication requires rapid follow-up)

Consider a waiting time between **elective** contrast-enhanced MRI with a gadolinium-based contrast agent and contrast-enhanced CT or (coronary) angiography with an iodine-based contrast medium in patients with **moderately reduced renal function** (eGFR 30-60 ml/min/1.73m<sup>2</sup>) of:

- Optimally 48 hours (near complete clearance of the previously administered gadolinium-based contrast agent)
- Minimally 16 hours (if the clinical indication requires rapid follow-up)

Consider a waiting time between **elective** contrast-enhanced MRI with a gadolinium-based contrast agent and contrast-enhanced CT or (coronary) angiography with an iodine-based contrast medium in patients with **severely reduced renal function** (eGFR < 30 ml/min/1.73m<sup>2</sup>) of:

- Optimally 168 hours (near complete clearance of the previously administered gadolinium-based contrast agent)
- Minimally 60 hours (if the clinical indication requires rapid follow-up)

When combining contrast-enhanced CT or (coronary) angiography with an iodine-based contrast medium and contrast-enhanced MRI with a gadolinium-based contrast agent on the same day in **emergency or life-threatening situations**, employ no waiting time and perform back-to-back examinations.

## 10.2 Analytical interference of contrast media with clinical laboratory tests

### Clinical question

How can contrast media interfere with commonly performed laboratory tests?

- 1) Iodine-based contrast media' interference
- 2) Gadolinium-based contrast agents' interference

### Recommendations

#### Blood Analysis

Be aware that the potential interference of contrast media on laboratory tests is crucial to prevent adverse patient work-up. As with all laboratory tests, the results should be interpreted in relationship with the patient's medical history and clinical examination.

Consult the laboratory specialist if there are any discrepancies between clinical presentation and laboratory tests.

Perform clinical laboratory testing prior to administrating contrast media or delay blood collection for non-emergency clinical laboratory testing\* for:

- At least 4 hours and optimally 12 hours after administration of the contrast medium in patients with normal kidney function (eGFR > 60 mL/min/1.73 m<sup>2</sup>)
- At least 16 hours and optimally 48 hours after administration of the contrast medium in patients with reduced kidney function (eGFR 30-60 mL/min/1.73 m<sup>2</sup>)
- At least 60 hours and optimally 168 hours after administration of the contrast medium in patients with reduced kidney function (eGFR < 30 mL/min/1.73 m<sup>2</sup>)

\*See also Module Multiple investigations with contrast media in patients with normal or reduced kidney function

### Urine Analysis

Perform urine clinical laboratory tests prior to contrast media administration. Another option is to delay urine collection for at least\*\*:

- At least 24 hours after administration of the contrast medium in patients with normal kidney function (eGFR > 60 mL/min/1.73 m<sup>2</sup>)
- At least 48 hours after administration of the contrast medium in patients with reduced kidney function (eGFR 30-60 mL/min/1.73 m<sup>2</sup>)
- At least 168 hours after administration of the contrast medium in patients with reduced kidney function (eGFR < 30 mL/min/1.73 m<sup>2</sup>)

\*\* based on near complete clearance of contrast media

## 11. Other safety measures

### 11.1 CM administration using power injectors

#### 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 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.

## 11.2 Optimal treatment of CM extravasation

### 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 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.

