ESUR Guidelines on **Contrast Agents**

European Society of Urogenital Radiology

10.0

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PREFACE

The Contrast Media Safety Committee is proud to present the 10th version of its Contrast Agent Guidelines. We started in 1994 and we have on average updated the booklet every 2 to 3 years. Over the years, more than 200,000 copies of the booklet have been printed and it has been translated into many languages. Although the contrast agents in current use have been on the market for many years, minor changes occur in their adverse reaction pattern and new observations are reported.

The 10th version of the Guidelines includes updated sections on acute adverse reactions, gadolinium contrast agents and other gadolinium issues, post contrast acute kidney injury (PC-AKI) and myeloma and contrast media. The CMSC has decided to regularize its use of the terms ‚contrast agent' and ‚contrast medium' and there is a brief section on terminology a the start of the Guidelines.

We hope that you like the new version, that it is helpful in your practice and that it will benefit all our patients. Comments and questions are welcome at esursecretary@esur.org

Contrast Media Safety Committee
March 2018
Henrik S. Thomsen, Chairman

NOTE: *CMSC guidelines are based on evidence in the literature whenever possible. Where there is insufficient published evidence, guidelines are based on clinical consensus within the Committee.*

Some CMSC guidelines may differ from the Summary of Product Characteristics (SPC, label), and/or guidelines drawn up by national and other radiological bodies.

LEGAL NOTICE: *The Committee and authors of the 10.0 contrast media guidelines claim no responsibility for the content of the translated versions of the guidelines.*

QUICK GUIDE TO THE CMSC CONTRAST AGENT GUIDELINES, VERSION 10

Terminology: Contrast agents and contrast media

SECTION A: GENERAL ADVERSE REACTIONS

Includes material on:

- Acute adverse reactions to iodine- and gadolinium-based contrast agents.
- Management of acute adverse reactions to iodine- and gadolinium-based and ultrasound contrast agents.
- Late adverse reactions.
- Thyrotoxicosis.
- Nephrogenic systemic fibrosis (NSF).

SECTION B: RENAL ADVERSE REACTIONS (POST CONTRAST ACUTE KIDNEY INJURY, PC-AKI)

Includes material on:

- Measurement of renal function.
- Renal adverse reactions to iodine- and gadolinium-based contrast agents.
- Metformin.

SECTION C: MISCELLANEOUS

All other topics for which the Committee has prepared guidelines, including:

- Pediatric use of contrast agents.
- Contrast medium extravasation.
- Pregnancy and lactation.
- Ultrasound contrast agents.
- Barium contrast media.
- Off-label use of contrast agents.

CONTENTS

TERMINOLOGY: CONTRAST AGENTS AND CONTRAST MEDIA

Terminology: Contrast agents and contrast media

A **contrast agent** is a substance which alters the contrast in images produced by any method. It is a general term which can be used for X-ray, MR and ultrasound contrast compounds.

A **contrast medium** is a substance which alters the contrast in X-ray images by altering transmission of the X-ray beam. This term should be reserved for X-ray contrast compounds, e.g. iodine-based, barium, air and carbon dioxide.

A. GENERAL ADVERSE REACTIONS

A.1. ACUTE ADVERSE REACTIONS

Definition: *An adverse reaction which occurs within 1 hour of contrast agent injection.*
The same acute adverse reactions are seen after iodine- and gadolinium-based contrast agents and after ultrasound contrast agents. The incidence is highest after iodine-based contrast media and lowest after ultrasound agents.

Classification

Acute reactions are either allergy-like, hypersensitivity reactions or chemotoxic responses. Allergy-like reactions may or may not be true IgE mediated allergy.

	Hypersensitivity/ Allergy-like	Grade (Ring and Messmer classification	Chemotoxic
Mild	Mild urticaria Mild itching Erythema	Grade 1 Grade 1 Grade 1	Nausea/mild vomiting Warmth/chills Anxiety Vasovagal reaction which resolves spontaneously
Moderate	Marked urticaria Mild bronchospasm Facial/laryngeal edema	Grade 1 Grade 2 Grade 2	Vasovagal reaction
Severe	Hypotensive shock Respiratory arrest Cardiac arrest	Grade 3 Grade 4 Grade 4	Arrythmia Convulsion

Note:

- *Be aware that what at first appears to be a mild reaction may develop into a more serious reaction.*
- *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 administation (Lalli effect).*
- *When a new contrast agent is first introduced to a department, adverse effects tend to be over-reported (Weber effect).*

A.1.1. Acute adverse reactions to iodine- and gadolinium-based contrast agents

Note: *Retrospective studies of the incidence of acute adverse reactions suffer from considerable under-reporting and are therefore unreliable.*

Risk factors for acute reactions	
Patient related	Patients with a history of: • Previous moderate or severe acute reaction (see classification above) to an iodine- or gadolinium-based contrast agent. • Asthma requiring medical treatment. • Atopy requiring medical treatment.
Contrast medium related	a) Iodine-based: • High-osmolality ionic contrast media. • There is no difference in the incidence of acute reactions between the non-ionic low-osmolar contrast agents and the non-ionic iso-osmolar contrast agents. • There is no difference in the incidence of acute adverse events among the non-ionic low-osmolar agents. b) Gadolinium-based: • The risk of a reaction is not related to the osmolality of the contrast agent: the low doses used make the osmolar load very small. • There is no difference in the incidence of acute adverse reactions among the gadolinium-based extracellular agents.
To reduce the risk of an acute reaction to iodine- and gadolinium-based agents	
For all patients	• Use a non-ionic iodine-based contrast medium.
For patients at increased risk of reaction (see risk factors above)	• Consider an **alternative test** not requiring a contrast agent of similar class. • For previous contrast agent reactors: use a different contrast agent, preferably after consultation with a specialist in drug allergy. • Premedication is not recommended because there is not good evidence of its effectiveness
Be prepared for an acute reaction	
For all patients	• Have the drugs and equipment for resuscitation readily available (see A.1.2.1.). • Keep the patient in a medical environment for 30 minutes after contrast agent injection.

A.1.2. Management of acute adverse reactions

The management is the same for acute adverse reactions after iodine- and gadolinium-based and ultrasound contrast agents.

A.1.2.1. Be prepared to treat acute adverse reactions

First line emergency drugs and equipment which should be in the examination room:

Oxygen
Adrenaline 1:1,000
Antihistamine H1 - suitable for injection
Atropine
ß2-agonist metered dose inhaler
I.V. fluids - normal saline or Ringer's solution
Anti-convulsive drugs (diazepam)
Sphygmomanometer
One-way mouth ‚breather' apparatus

- Resuscitation trolley should be available in the department.
- Emergency numbers for the hospital resuscitation team should be in the examination room.
- Medical and technical staff should receive regular education in the management of acute adverse reactions and in resuscitation technique.
- Equipment for collecting blood for tryptase and histamine measurement should be readily available.
- Keep the patient in a medical environment for 30 minutes after contrast agent injection.

A.1.2.2. Simple guidelines for first line treatment of acute reactions to all contrast agents

When an acute reaction occurs, check for the following:

- Skin erythema, urticaria (undress the patient to inspect the whole body).
- Nausea, vomiting.
- Decreased blood pressure, abnormal heart rate.
- Dyspnea, bronchospasm (requires auscultation for reliable diagnosis).

Nausea/vomiting
Transient: supportive treatment.
Severe, protracted: appropriate antiemetic drugs should be considered.
Note: *severe vomiting may occur during anaphylaxis.*

Urticaria
Scattered, transient: supportive treatment including observation.
Scattered, protracted or generalized or angioedema: appropriate H1-antihistamine should be given intramuscularly or intravenously. Drowsiness and/or hypotension may occur. After administration of anithistamines, the patient may no longer be insured to drive a car or operate machinery.

Bronchospasm
1. Oxygen by mask (6-10 l/min).
2. β-2-agonist metered dose inhaler (2-3 deep inhalations).
3. Adrenaline

Normal blood pressure
Intramuscular: 1:1,000, 0.1-0.3 ml (0.1-0.3 mg) [use smaller dose in patients with coronary artery disease or elderly patients].
In pediatric patients: 50 % of adult dose to pediatric patients between 6 and 12 years old and 25 % of adult dose to pediatric patients below 6 years old - repeat as needed.
Decreased blood pressure
Intramuscular: 1:1,000, 0.5 ml (0.5 mg).
In pediatric patients: 6-12 years: 0.3 ml (0.3 mg) intramuscularly
< 6 years: 0.15 ml (0.15 mg) intramuscularly

Laryngeal edema
1. Oxygen by mask (6-10 l/min).
2. Intramuscular adrenaline (1:1,000), 0.5 ml (0.5 mg) for adults - repeat as needed.
   In pediatric patients: 6-12 years: 0.3 ml (0.3 mg) intramuscularly
   < 6 years: 0.15 ml (0.15 mg) intramuscularly

Hypotension
Isolated hypotension
1. Elevate patient's legs.
2. Oxygen by mask (6-10 l/min).
3. Intravenous fluid: rapidly, normal saline or Ringer's solution up to 2 litres.
4. If unresponsive: adrenaline: 1:1,000, 0.5 ml (0.5 mg) intramuscularly - repeat as needed.
   In pediatric patients: 6-12 years: 0.3 ml (0.3 mg) intramuscularly
   < 6 years: 0.15 ml (0.15 mg) intramuscularly

Vasovagal reaction (hypotension and bradycardia)

1. Elevate patient's legs.
2. Oxygen by mask (6-10 l/min).
3. Atropine 0.6-1.0 mg intravenously - repeat if necessary after 3-5 min, to 3 mg total (0.04 mg/kg) in adults. In pediatric patients give 0.02 mg/kg intravenously (max 0.6 mg per dose) - repeat if necessary to 2 mg total.
4. Intravenous fluids: rapidly, normal saline or Ringer's solution, up to 2 litres.
5. If the patient does not respond to these measures, treat as for anaphylaxis.

Generalized anaphylactoid reaction

1. Call for resuscitation team.
2. Suction airway as needed.
3. Elevate patient's legs if hypotensive.
4. Oxygen by mask (6-10 l/min).
5. Intramuscular adrenaline (1:1,000), 0.5 ml (0.5 mg) in adults - repeat as needed.
   In pediatric patients: 6-12 years: 0.3 ml (0.3 mg) intramuscularly
   < 6 years: 0.15 ml (0.15 mg) intramuscularly
6. Intravenous fluids (e.g. normal saline, Ringer's solution) up to 2 liltres.
7. H1-blocker e.g. diphenhydramine 25-50 mg intravenous.

A.1.2.3. After a moderate or severe acute adverse reaction to a contrast agent

Test for evidence of allergy

- Take blood samples for estimation of histamine and tryptase at 1 and 2 hours after contrast agent administration and at 24 hours if the patient is still in the hospital.
- 1 to 6 months after the reaction the patient should be referred to a specialist in drug allergy to have skin testing. Prick and intradermal tests should be used to check for evidence of true allergy to the contrast agent and for evidence of cross-reactivity to other contrast agents.
- An example of a suitable letter for the patient to take to the allergy consultation can be found in section D of these guidelines.

Record the reaction

- Record the contrast agent name and dose and the details of the reaction and its treatment in the patient's records.
- Record the information about the reaction (see above) in the hospital adverse events register.
- If the reaction is severe or unusual, report it to the national pharmacovigilance authority.

A.1.2.4. Review of treatment protocols

Radiologists and their staff should review treatment protocols regularly (e.g. at 12 monthly intervals), so that each can accomplish their role efficiently. Knowledge, training, and preparation are crucial for guaranteeing appropriate and effective treatment if there is an adverse contrast related event.

A.1.3. Warming iodine-based contrast medium before administration

- Appears to make the patient more comfortable, based on clinical observation.
- Reduces viscosity and may reduce the risk of contrast medium extravasation.
- May reduce the rate of general adverse events, but data on this is limited.
- Is widely regarded as best practice.

A.1.4. Extravascular administration of an iodine-based contrast medium

- When absorption or leakage into the circulation is possible, take the same precautions as for intravascular administration.

A.1.5. Fasting before administration of contrast agents

Fasting before intravenous administration of contrast agents dates from the time when high-osmolar iodine-based contrast media were used and many patients vomited. Fasting is not recommended before administration of low- or iso-osmolar non-ionic iodine-based contrast media or of gadolinium-based agents.

A.2. LATE ADVERSE REACTIONS

Definition	A late adverse reaction to intravascular iodine-based contrast medium is defined as a reaction which occurs 1 h to 1 week after contrast medium injection.
Reactions	**Skin reactions** similar in type to other drug induced eruptions occur. Maculopapular rashes, erythema, swelling and pruritus are most common. Most skin reactions are mild to moderate and self-limiting. A variety of late symptoms (e.g., nausea, vomiting, headache, musculoskeletal pains, fever) have been described following contrast medium, but many are not related to the contrast medium.
Risk factors for skin reactions	• Previous late contrast medium reaction • Interleukin-2 treatment • Use of non-ionic dimers
Management	Symptomatic and similar to the management of other drug-induced skin reactions e.g. antihistamines, topical steroids and emollients.
Recommendations	Patients who have had a previous contrast medium reaction, or who are on interleukin-2 treatment should be advised that a late skin reaction is possible and that they should contact a doctor if they have a problem. Patch and delayed reading intradermal tests may be useful to confirm a late skin reaction to contrast medium and to study cross-reactivity patterns with other agents. To reduce the risk of repeat reaction, use a contrast medium other than that which precipitated the first reaction. Avoid agents which have shown cross-reactivity on skin testing. Drug prophylaxis is generally not recommended.

Note: *Late skin reactions of the type which occur after iodine-based contrast media have not been described after gadolinium-based and ultrasound contrast media.*

A.3. VERY LATE ADVERSE REACTIONS

Definition: *an adverse reaction which usually occurs more than 1 week after contrast agent injection.*

Type of reaction	
Iodine-based contrast media	• Thyrotoxicosis
Gadolinium-based contrast agents	• Nephrogenic systemic fibrosis

A.3.1. Very late adverse reactions to iodine-based contrast media: thyrotoxicosis

At risk	Patients with untreated Graves' disease. Patients with multinodular goiter and thyroid autonomy, especially if they are elderly and/or live in an area of dietary iodine deficiency.
Not at risk	Patients with normal thyroid function.
Recommendations	**Iodine-based contrast media should not be given to patients with manifest hyperthyroidism.** • In patients suspected of being at risk of thyrotoxicosis, TSH measurement may be helpful. • In selected high-risk patients, prophylactic treatment may be given by an endocrinologist. • Patients at risk should be closely monitored by endocrinologists after iodine-based contrast medium injection. • Intravenous cholangiographic contrast media should not be given to patients at risk.

A.3.2. Very late adverse reactions to gadolinium-based contrast agents: nephrogenic systemic fibrosis (NSF)

Diagnosis	A diagnosis of nephrogenic systemic fibrosis (NSF) should only be made if the Yale NSF Registry clinical and histopathological criteria are met (J Am Acad Dermatol 2011; 65: 1095-1106). The association between nephrogenic systemic fibrosis (NSF) and gadolinium-based contrast agents was recognized in 2006.
Clinical features	*Onset* can be from the day of exposure for up to 2-3 months. Rarely, it can occur years after exposure.
	Early changes are pain, pruritus, and swelling and erythema of the skin, which usually start in the legs.
	Later changes include fibrotic thickening of the skin and subcutaneous tissues and limb contractures may occur. Fibrosis of internal organs, e.g. muscle, diaphragm, heart, liver, lungs may also occur. There may be *death* if involvement of internal organs is severe.
RISK FACTORS	
Patient related	• Reduced renal function, particularly if eGFR < 15 ml/min/1.73 m2. • Patients on dialysis.
Contrast agent related	• Gadodiamide was responsible for most reported NSF cases. • NSF also occurred after gadopentetate dimeglumine and gadoversetamide. • Risk increases with increasing contrast agent dose, but NSF may occur after a single dose.
Estimated incidence in patients with severe renal failure	• 3-18 % after gadodiamide. • 0.1-1 % after gadopentetate dimeglumine.

GADOLINIUM-BASED CONTRAST AGENTS: Risk classification (based on laboratory data) and recommendations	
Highest risk of NSF	
Contrast agents	Gadodiamide (Omniscan®) *Ligand*: Non-ionic linear chelate (DTPA-BMA) Gadopentetate dimeglumine (Magnevist® *Ligand:* Ionic linear chelate (DTPA) Gadoversetamide (Optimark®) *Ligand:* Non-ionic linear chelate (DTPA-BMEA)
Recommendations	• European Medicines Agency (EMA) has suspended intravenous use of all high-risk agents (Omniscan®, Magnevist®) and the Marketing Authorization Holder has withdrawn Optimark® from the European market. • EMA states that Magnevist® may be used for arthrography. • CMSC supports these recommendations.
Intermediate risk of NSF	
Contrast agents	Gadobenate dimeglumine (Multihance®) *Ligand:* Ionic linear chelate (BOPTA) *Special feature:* It is a combined extracellular and liver specific agent with 2-3% albumin binding. In man ~4% is excreted via the liver. Gadoxetate disodium (Primovist®, Eovist®) *Ligand:* Ionic linear chelate (EOB-DTPA)
Recommendations	• EMA states that intermediate risk agents (Multihance®, Primovist®) are approved for hepato-biliary imaging only. • CMSC supports this recommendation.

Lowest risk of NSF	
Contrast agents	Gadobutrol (Gadovist®, Gadavist®) *Ligand:* Non-ionic cyclic chelate (BT-DO3A) Gadoterate meglumine (Dotarem®, Magnescope® plus generic products) *Ligand:* Ionic cyclic chelate (DOTA) Gadoteridol (Prohance®) *Ligand*: Non-ionic cyclic chelate (HP-DO3A)
Recommendations	• These agents should be used with CAUTION in patients with GFR < 30 ml/min. There should be at least 7 days between two injections. • Pregnant women: these agents can be used to give essential diagnostic information. • Lactating women: discarding the breast milk in the 24 hours after contrast medium is not considered necessary, but the patient can discuss with the doctor whether she wishes to do this. • Laboratory testing of renal function (eGFR) is **not mandatory.**
Recommendations for all patients	Never deny a patient a clinically well-indicated enhanced MR-examination. In all patients use the smallest amount of contrast medium necessary for a diagnostic result. Always record the name and dose of the contrast agent used in the patient records.

B. RENAL ADVERSE REACTIONS (POST-CONTRAST ACUTE KIDNEY INJURY, PC-AKI)

Definitions:

Post-contrast acute kidney injury (PC_AKI) *is defined as an increase in serum creatinine > 0.3 mg/dl (or > 26.5 µmol/l), or > 1.5 times baseline, within 48-72 hours of intravascular administration of a contrast agent.*

Intra-arterial injection with first pass renal exposure *indicates that contrast agent reaches the renal arteries in a relatively undiluted form, e.g. injection into the left heart, thoracic and suprarenal abdominal aorta or the renal arteries.*

Intra-arterial injection with second pass renal exposure *indicates that contrast agent reaches the renal arteries after dilution either in the pulmonary or peripheral circulation, e.g. injection into the right heart, pulmonary artery, carotid, subclavian, coronary, mesenteric or infra-renal arteries.*

B.1. MEASUREMENT OF RENAL FUNCTION

- **Estimated glomerular filtration rate (eGFR), calculated from the serum creatinine, is the recommended method to estimate renal function before contrast agent administration.**
- **In adults ≥ 18 years the CKD-EPI formula is recommended to calculate eGFR.**

  eGFR (ml/min/1.73 m^2) =

  Female sCr ≤ 62 µmol/l: $144 \times (sCr / 62)^{-0.329} \times 0.993^{Age}$

  Female sCr > 62 µmol/l: $144 \times (sCr / 62)^{-1.209} \times 0.993^{Age}$

  Male sCr ≤80 µmol/l: $141 \times (sCr / 80)^{-0.411} \times 0.993^{Age}$

  Male sCr > 80 µmol/l: $141 \times (sCr / 80)^{-1.209} \times 0.993^{Age}$

  (sCr in µmol/l; age in years)

  All equations x 1.159 if African American race.
- **In children, the revised Schwartz formula is recommended to calculate eGFR**

  eGFR (ml/min/1.73 m^2) = 36.5 x length / sCr

  (sCr in µmol/l; length in cm)

Note: *Neither serum nor plasma creatinine is an ideal indicator of renal function and may miss decreased renal function.*

B.2. RENAL ADVERSE REACTIONS TO IODINE-BASED CONTRAST MEDIA

RISK FACTORS FOR PC-AKI	
Patient related	eGFR less than 45 ml/min/1.73 m^2 before intra-arterial contrast medium administration with first pass renal exposure or in ICU patients. eGFR less than 30 ml/min/1.73 m^2 before intravenous contrast medium or intra-arterial contrast medium administration with second pass renal exposure. Known or suspected acute renal failure.
Procedure related	Intra-arterial contrast medium administration with first pass renal exposure. Large doses of contrast medium given intra-arterially with first pass renal exposure. High-osmolality contrast media. Multiple contrast medium injections within 48-72 hours.

B.2.1. Time of Referral

ELECTIVE EXAMINATION

MEASUREMENT OF RENAL FUNCTION

- **Measure eGFR before administering intravascular iodine-based contrast medium**

  Either (a) In all patients
  or (b) In patients who have a history of
  - Renal disease (eGFR < 60 ml/min/1.73 m^2)
  - Kidney surgery
  - Proteinuria
  - Hypertension
  - Hyperuricemia
  - Diabetes mellitus

- **Timing of eGFR measurement**

- Within 7 days before contrast medium administration in patients with an acute disease, an acute deterioration of a chronic disease or who are hospital inpatients.
- Within 3 months before contrast medium administration in all other patients.

EMERGENCY EXAMINATION

Identify at-risk patients (see above) if possible:

- Determine eGFR if the procedure can be deferred until the result is available without harm to the patient.
- If eGFR cannot be obtained, follow the protocols for patients with eGFR less than 45 ml/min/1.73 m^2 for intra-arterial administration with first pass renal exposure and eGFR less than 30 ml/min/1.73 m^2 for intravenous administration and intra-arterial administration with second pass renal exposure as closely as clinical circumstances permit.

B.2.2. Before the Examination

ELECTIVE EXAMINATION	
At-risk patients (see above)	• Consider an alternative imaging method not using iodine-based contrast media. • Intravenous saline and bicarbonate protocols have similar efficacy for preventive hydration. • For intravenous contrast medium and intra-arterial contrast medium administration with second pass renal exposure hydrate the patient *either* (a) with intravenous sodium bicarbonate 1.4 % (or 154 mmol/l in dextrose 5 % water): 3 ml/kg/h for 1 hour before contrast medium *or* (b) with intravenous saline 0.9 % 1 ml/kg/hr for 3-4 hours before and 4-6 hours after contrast medium. • For intra-arterial contrast medium administration with first pass renal exposure hydrate the patient *either* with (a) intravenous sodium bicarbonate 1.4 % (or 154 mmol/l in dextrose 5 % water): 3 ml/kg/h for 1 hour before followed by 1 ml/kg/hr for 4-6 hours after contrast medium *or* (b) with intravenous saline 0.9 % for 3-4 hours before and 4-6 hours after contrast medium. • The clinician responsible for patient care should individualize preventive hydration in patients with severe congestive heart failure (NYHA grade 3-4) or patients with end-stage renal failure (eGFR < 15 ml/min/1.73 m^2). • Oral hydration is not recommended as the sole method of preventive hydration.

EMERGENCY EXAMINATION	
At-risk patients (see above)	• Consider an alternative imaging method not using iodine-based contrast media. • Use preventive hydration before contrast medium administration (see ‚Elective examination' for protocols).

B.2.3. Time of examination

All patients	• Use low- or iso-osmolar contrast media. • Use the lowest dose of contrast medium consistent with a diagnostic result. • For intra-arterial contrast medium administration with first pass renal exposure, keep *either* the ratio CM dose (in gram I) / *absolute* eGFR (in ml/min) < 1.1 *or* the ratio CM volume (in ml) / eGFR (in ml/min/1.73 m^2) < 3.0, when using contrast medium concentration of 350 mgI/ml.

B.2.4. After the Examination

At-risk patients	• Continue preventive hydration if appropriate (see protocols above). • Determine eGFR 48 hours after contrast medium administration. • If at 48 hours there is a diagnosis of PC-AKI, monitor the patient clinically for at least 30 days and determine eGFR at regular intervals.

Note: *No **pharmacological prophylaxis** (with statins, renal vasodilators, receptor antagonists of endogenous vasoactive mediators or cytoprotective drugs) has been shown to offer consistent protection against PC-AKI.*

B.2.5. Multiple myeloma patients

- Multiple myeloma patients with normal renal function are not at increased risk of PC-AKI provided that they are well hydrated and that low- or iso-osmolar iodine-based contrast media are used.
- Multiple myeloma patients often have reduced renal function, and such patients are at increased risk of PC-AKI.
- Multiple myeloma patients often have hypercalcemia which can increase the risk of kidney damage. Correction of hypercalcemia before contrast medium administration should be discussed with the hematologist.
- Assessment for Bence Jones proteinuria before contrast medium administration is not necessary.

B.3. RENAL ADVERSE REACTIONS TO GADOLINIUM-BASED CONTRAST MEDIA

MR-EXAMINATIONS

- The risk of PC-AKI is very low when gadolinium-based contrast agents are used in approved doses.
- In patients with reduced renal function refer to ESUR guidelines on NSF, A.3.2.

RADIOGRAPHIC EXAMINATIONS

- Gadolinium-based contrast agents are not approved for radiographic examinations.
- Gadolinium-based contrast agents should not be used for radiographic examinations in patients with renal impairment (eGFR < 60 ml/min/1.73 m^2).
- Gadolinium-based contrast agents are more nephrotoxic than iodine-based contrast media in equivalent X-ray attenuating doses

B.4. PATIENTS WITH DIABETES MELLITUS TAKING METFORMIN

B.4.1. Iodine-based contrast media

1. Patients with eGFR > 30 ml/min/1.73 m^2 and no evidence of AKI, receiving either intravenous contrast medium or intra-arterial contrast medium with second pass renal exposure: continue taking metformin normally.
2. Patients
   (a) with eGFR < 30 ml/min/1.73 m^2 receiving intravenous contrast medium, or intra-arterial contrast medium with second pass renal exposure.
   (b) Receiving intra-arterial contrast medium with first pass renal exposure.
   (c) With AKI: Stop taking metformin from the time of contrast medium administration. Measure eGFR within 48 hours and restart metformin if renal function has not changed significantly.

B.4.2. Gadolinium-based contrast media

No special precautions are necessary when diabetic patients on metformin are given gadolinium-based contrast agents as the risk of PC-AKI is very low.

B.5. DIALYSIS AND CONTRAST MEDIUM ADMINISTRATION

All iodine- and gadolinium-based contrast agents can be removed by hemodialysis or peritoneal dialysis.
However, there is no evidence that hemodialysis protects patients with impaired renal function from post contrast acute kidney injury or nephrogenic systemic fibrosis.
In all patients, avoid osmotic and fluid overload.
To avoid the risk of NSF refer to A.3.2.

PATIENTS ON DIALYSIS	
Patients on hemodialysis	**Iodine-based contrast medium** • Correlation of time of the contrast medium injection with the hemodialysis session is unnecessary. • Extra hemodialysis session to remove contrast medium is unnecessary. **Gadolinium-based contrast agent** • Correlation of time of the contrast agent injection with the hemodialysis session is recommended. • Extra hemodialysis session to remove contrast agent as soon as possible after it has been administered is recommended.
Patients on continuous ambulatory peritoneal dialysis	**Iodine-based contrast medium** Hemodialysis to remove the contrast medium is unnecessary. **Gadolinium-based contrast agent** The need for hemodialysis should be discussed with the referring physician.

B.6. CAN IODINE- AND GADOLINIUM-BASED CONTRAST AGENTS SAFELY BE GIVEN ON THE SAME DAY FOR ROUTINE EXAMINATIONS?

Efficient practice may involve giving iodine- and gadolinium-based contrast agents for enhanced CT and MR on the same day. To reduce any potential for nephrotoxicity the following are recommended:

1. **Patients with normal renal function or moderately reduced (GFR > 30 ml/min/1.73 m²).**
   75 % of both gadolinium- and iodine-based contrast agents are excreted by 4 hours after administration. There should be 4 hours between injections of iodine- and gadolinium-based contrast agents.
2. **Patients with severely reduced renal function (GFR < 30 ml/min/1.73 m² or on dialysis).**
   There should be 7 days between injections of iodine- and gadolinium-based contrast agents.

Note: *Gadolinium-based contrast agents attenuate X-rays well and may be misinterpreted on CT when they have been excreted into the urinary tract. For abdominal examinations, enhanced CT should be done before enhanced MR. For chest and brain examinations, either CT or MR may be done first.*

B.7. HOW LONG SHOULD THERE BE BETWEEN TWO IODINE-BASED CONTRAST MEDIUM INJECTIONS FOR ROUTINE EXAMINATIONS?

1. **Patients with normal or moderately reduced renal function (GFR > 30 ml/min/1.73 m²).**
   75 % of iodine-based contrast medium is excreted by 4 hours after administration. There should be 4 hours between injections of iodine-based contrast medium.
2. **Patients with severely reduced renal function (GFR < 30 ml/min/1.73 m²).**
   There should be 48 hours between injections of iodine-based contrast medium.
3. **Patients on dialysis.**
   If there is remnant renal function there should be at least 48 hours between injections of iodine-based contrast medium.

B.8. HOW LONG SHOULD THERE BE BETWEEN TWO GADOLINIUM-BASED CONTRAST AGENT INJECTIONS FOR ROUTINE EXAMINATIONS?

1. **Patients with normal or moderately reduced renal function (GFR > 30 ml/min/1.73 m²).**
   75 % of extracellular gadolinium-based contrast agents are excreted by 4 hours after administration.
   There should be 4 hours between injections of gadolinium-based contrast agent.
2. **Patients with severely reduced renal function (GFR < 30 ml/min/1.73 m²) or on dialysis.**
   There should be 7 days between injections of gadolinium-based contrast agent

C. MISCELLANEOUS

C.1. CONTRAST MEDIUM EXTRAVASATION

Type of injuries	• Most injuries are minor. • Severe injuries include skin ulceration, soft-tissue necrosis, and compartment syndrome.
RISK FACTORS	
Technique-related	• Use of a power injector. • Less optimal injection sites including lower limb and small distal veins. • Large volume of contrast medium. • High-osmolar contrast media. • High-viscosity contrast media.
Patient-related	• Inability to communicate. • Fragile or damaged veins. • Arterial insufficiency. • Compromised lymphatic and/or venous drainage. • Obesity.
To reduce the risk	• Intravenous technique should always be meticulous using an appropriate sized plastic cannula placed in a suitable vein to handle the flow rate used during the injection. • Consider use of cannulas with sideholes. • Test injection with normal saline. • Use non-ionic iodine-based contrast medium.

Management	• Documenting the extravasation with a plain radiograph, CT scan or MR scan of the affected region may be helpful.
	• Conservative management is adequate in most cases.
	  • Limb elevation
	  • Ice packs
	  • Careful monitoring.
	• If a serious injury is suspected, seek the advice of a surgeon.

C.2. PULMONARY EFFECTS OF IODINE-BASED CONTRAST MEDIA

Pulmonary adverse effects	• Bronchospasm. • Increased pulmonary vascular resistance. • Pulmonary edema.
Patients at high risk	• History of asthma. • History of pulmonary hypertension. • Incipient cardiac failure.
To reduce the risk of pulmonary adverse effects	• Use low- or iso-osmolar contrast media. • Avoid large doses of contrast media.

C.3. EFFECTS OF CONTRAST MEDIA ON BLOOD AND ENDOTHELIUM

C.3.1. Thrombosis

C.3.1.1. Iodine-based contrast media

The clinically important adverse effect of iodine-based contrast media on blood and endothelium is thrombosis.
It is recognized that:

- All contrast media have anticoagulant properties, especially ionic agents.
- High-osmolar ionic contrast media may induce thrombosis due to endothelial damage, particularly in phlebographic procedures.
- Drugs and interventional devices that decrease the risk of thromboembolic complications during interventional procedures minimize the importance of the effects of contrast media.

Guidelines

- Meticulous angiographic technique is mandatory and is the most important factor in reducing thromboembolic complications.
- Low- or iso-osmolar contrast media should be used for diagnostic and interventional angiographic procedures including phlebography.

C.3.2. Sickle Cell Disease

C.3.2.1. Iodine-based contrast media

- In patients with sickle cell disease, high-osmolar iodine-based contrast media may cause red cell sickling, leading to hemolysis and small vessel occlusion.
- Low- or iso-osmolar iodine-based contrast media produce no more adverse events in patients with sickle cell disease than in the normal population.

Guidelines

- Use low- or iso-osmolar iodine-based contrast media.
- Hydrate patients before contrast medium administration.

C.3.2.2. Gadolinium-based contrast media

- The smaller doses of gadolinium-based contrast agents compared to iodine-based contrast media reduce the osmolar load, so contrast agent osmolality is unlikely to be a significant problem.
- No adverse events suggestive of red blood cell sickling have been reported after gadolinium-based contrast agents.

Guidelines

- Use any gadolinium-based contrast agent.
- No special preparation is necessary.

C.4. CONTRAST AGENTS AND CATECHOLAMINE PRODUCING TUMORS (PHEOCHROMOCYTOMA AND PARAGANGLIOMA)

Preparation

a) Before intravenous iodine- or gadolinium-based contrast agent: no special preparation is required.
b) Before intra-arterial iodine-based contrast medium:
α and β-adrenergic blockade with orally administered drugs under the supervision of the referring physician is recommended.

Type of contrast agent which should be used

- Iodine-based: non-ionic agent.
- Gadolinium-based: any agent.

C.5. PREGNANCY AND LACTATION

	Iodine-based contrast media	Gadolinium-based contrast agents
Pregnancy	a)In exceptional circumstances, when radiographic examination is essential, iodine-based contrast media may be given to the pregnant female. b) Following administration of iodine-based contrast media to the mother during pregnancy, thyroid function should be checked in the neonate during the first week.	a) When there is a very strong indication for enhanced MR, the smallest possible dose of a macrocyclic gadolinium contrast agent (see A.3.2. Agents with lowest risk of NSF) may be given to the pregnant female. b) Following administration of gadolinium-based agents to the mother during pregnancy, no neonatal tests are necessary.
Lactation	Breast feeding may be continued normally when iodine-based contrast media is given to the mother.	Breast feeding may be continued normally when macrocyclic gadolinium-based contrast agents are given to the mother.
Pregnant or lactating mother with renal impairment	See renal adverse reactions (B.2.). No additional precautions are necessary for the fetus or neonate.	Do not administer gadolinium-based contrast agents.