A. GENERAL ADVERSE REACTIONS

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	Chemotoxic

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

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. ?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 intravenously.

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

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 m^2. 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.