

## Radiographic and magnetic resonances contrast agents: Essentials and tips for safe practices

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### Abstract

With extended and continued expansion of medical imaging utilization in modern medical practice over last decade, radiologists as well as other faculty staff dealing with radiographic and magnetic resonances contrast media (CM) have to be well oriented with their potential hypersensitivity reactions and recognize high-risk groups liable to develop it and enable early recognition. Radiologists and other medical staff involved in administration and dealing with CM have to be ready to implement prompt, practical and effective management plan to deal with these scenarios should they emerge. Strategies to prevent potential contrast-induced acute and delayed renal injuries have to be routinely exercised. Paying attention to the pregnant and nursing women, pediatrics, diabetics, as well as other fragile populations is of utmost importance for patient safety during contrast administrations. Radiologists should play a pivotal role in orienting patients about necessity to use CM for their imaging studies, in case it is needed, and assure them about its safety. Moreover, they have to be oriented with the medico-legal issues related to use of CM. These will pay as improved patient safety as well as safe daily working environment at different levels of radiology practices.

**Key words:** Radiographic; Magnetic resonances; Contrast; Safe practice; Medico-legal

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**Core tip:** Radiologists have to be oriented with the potential hypersensitivity reactions of radiographic and magnetic resonances contrast media (CM) and able to recognize high-risk groups liable to develop such reactions. Effective management plans have to be ready to implement should these scenarios emerge. Strategies to prevent potential contrast-induced acute and delayed renal injuries have to be exercised. Caring

for special considerations as well as other fragile populations is of utmost importance for patients' safety. Moreover, radiologists should be oriented with the medico-legal issues related to use of CM. These will be conveyed as improved patients' safety and safe radiology practices.

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## INTRODUCTION

Advances in the field of medical imaging over last decade, notably for multi-detector computed tomography (MDCT) and magnetic resonances imaging (MRI) have been associated with increased use of contrast media (CM). Likewise, the extended spectrum of therapeutic interventional procedures in different body organs, using imaging guidance tools, has expanded the use of CM.

Although CM are generally safe, their allergy-like reactions may be mild needing just observation and patient reassurance or may rarely result in potential life threatening conditions. These situations impose a day to day challenge for radiologists and allied medical staff at different levels of radiology practices. Hence, radiologists and medical personnel involved in CM administration have to be oriented to the justifications for their use and stratification of risk factors that increase the likelihood of patients to develop adverse reactions to CM. Moreover, they have to be able to recognize these adverse reactions once they ensue and promptly as well as effectively deal with it for patient safety. Besides, radiology practice personnel have to familiarize themselves to the medico-legal caveats associated with their practices. They should develop their own protocols for safe practice should CM administration be required. This review aims to highlight an updated discussion about these aforementioned hot issues related to use of CM in our daily work.

## CM: ESSENTIAL KNOWLEDGE

CM are pharmaceutical formulas that have been used to supplement the capabilities of various medical imaging modalities. They can be administered *via* different routes; the most widely used, and subject of the current review, is the intravenous access.

Describing the different types, classifications, uses and rout of administrations is beyond the scope of this review. However, a summary of the essential knowledge, for every radiologist, about current available CM will be underscored briefly in the next paragraphs.

Based on the differential attenuation of iodine by ionizing radiation, iodine-based contrast agents are used for contrast-enhanced radiographic and MDCT procedures<sup>[1]</sup>.

Physico-chemically; iodine-based contrast agents may be grouped according to their: (1) ionicity (to ionic or nonionic CM); (2) osmolality into high osmolar CM (HOCM), low-osmolar (LOCM), or iso-osmolar (IOCM); and (3) the number of benzene rings (either monomeric or dimeric CM)<sup>[2]</sup>. Owing to the contemporary implementation of non-ionic IOCM and LOCM in clinical imaging practices worldwide with withdrawal of HOCM, our discussion on iodinated CM will focus onto the non-ionic (iso- and low-osmolar) CM.

On the other hand, gadolinium-based contrast agents (GBCAs) are used to enhance MR examinations, thanks to their ability to alter the relaxivity of infused tissues; largely<sup>[3]</sup>. However, they can provide physiologic data derived from proton density and flow within the induced field depending of the weighting of the image<sup>[4]</sup>.

Likewise, GBCAs are commonly grouped according to their: (1) pharmacokinetics (either extracellular or organ specific and the extracellular GBCAs may be further sub-classified into blood-pool agents and; interstitial extracellular agents); (2) the chelating ligand molecular design (either; macrocyclic or linear); and (3) their ionicity (ionic or nonionic)<sup>[2]</sup>.

## EPIDEMIOLOGY OF CM REACTIONS

In general, CM (both iodinated and gadolinium based) are safe drugs with very low incidence of adverse reactions<sup>[5]</sup>. Hypersensitivity reactions to CM are generally sporadic and unpredictable<sup>[2,5-7]</sup>. The incidences of mild to moderate CM reactions are commoner for iodinated CM than gadolinium-based chelates<sup>[2,6,7]</sup>. Moreover, the hypersensitivity to non-ionic iodinated CM is far rare compared to their ionic correspondents<sup>[2,5,6]</sup> (Table 1). highlights the salient predisposing risk factors and populations at risk for development of acute adverse reaction to CM. Age extremes populations are at high risk for developing mild to moderate hypersensitivity reactions to CM<sup>[8,9]</sup>. The incidence of severe sensitivity reaction doesn't differ between different CM agents including the gadolinium chelates<sup>[10,11]</sup>.

An overall major determinant of patient's intolerance to CM administration is a history of a previous severe reaction to a contrast agent<sup>[8,9]</sup>. This increases the likelihood of the patient to develop a life-threatening hypersensitivity reaction by 3-6 fold<sup>[2]</sup>. Other major determinants are active generalized allergic tendencies (*e.g.*, asthma, hay fever, *etc.*) and compromised renal functions<sup>[5,10,12]</sup>. However, controlled atopies; including asthma don't preclude patients to have intravenous CM when necessary<sup>[12]</sup>.

Recognizing these factors could be achieved *via* scrutinizing patient's history cautiously. Thomsen<sup>[2]</sup> proposed a simplified questionnaire to simply identify high-risk patients liable to suffer CM-induced renal complications by asking the patient seven critical questions: Whether the patient had or has: (1) renal disease; (2) previous renal surgery; (3) proteinuria; (4) diabetes mellitus; (5) hypertension; (6) gout; and (7) recent administration of nephrotoxic drugs]. The authors

**Table 1 Risk factors that predispose patients to contrast medium reactions**

Patients with a prior history of allergy to CM (3-6 folds)
Patients with a prior history of allergic reactions to drugs and foods
Patients with generalized atopic tendencies ( <i>e.g.</i> , asthma and hay fever)
Dehydration states
Age extremes (less than 5 yr and older than 60 yr)
Serious illness and chronic debilitating conditions, <i>e.g.</i> , CVS diseases and renal failure
Anemia
Certain co-medications, <i>e.g.</i> , $\beta$ -blockers and metformin
Malignancies
Patient's anxiety due to public concerns about CM-induced reaction

CM: Contrast media; CVS: Cardiovascular.

**Table 2 Co-morbidities indicating renal profile checkup prior to contrast agent administration**

Age extremes	Older than 60 yr and less than 5 yr
History of relevant renal disorders	Anatomic variations: Solitary kidney and horse-shoe kidney
	Renal surgeries
	Renal endangering medications, <i>e.g.</i> , NSAIDs and chemotherapy
	Renal-induced nephropathy (prior)
	History of prior renal dialysis
Nephropathy-associated chronic diseases	Renal malignancies
	<i>E.g.</i> , uncontrolled DM, hypertension and hyperuricemia
Drugs interfering with renal excretions	Metformin

NSAIDs: Nonsteroidal antiinflammatory drugs; DM: Diabetes mellitus.

thought that adding two more critical questions, which are (1) whether the patient had underwent a contrast-enhanced imaging study or not? and (2) if any, what was his/her experience with it? May expand the benefit of this questionnaire to be more global for identification of most high-risk patients are prone to develop CM induced hypersensitivity.

## PATHOGENESIS OF CM HYPERSENSITIVITY

In spite of different postulations, the exact nature of CM hypersensitivity reactions is not clearly understood yet. The osmolality and chemotoxicity of an iodinated contrast agent are thought to be major determinants of its adverse reaction liability<sup>[13,14]</sup>.

For immediate hypersensitivity reactions, both the Ig-G mediated mechanisms (allergy-like) and the unpredictable non-allergic (idiosyncratic) mechanisms, thought to depend on the chemotoxic effects and physico-chemical properties of the agent, are plausible. For either pathway, cell-membrane injury of basophils and mast cell with subsequent release of histamine;

bradykinins; and other inflammatory mediators is the main event<sup>[14,15]</sup>. Also, activation of the clotting factor XII with subsequent activation of kinin system as well as cyclo-oxygenase and lipoxygenase inflammatory pathways and production of bradykinin, prostaglandins and leukotrienes is thought to mediate the CM induced respiratory and cardiovascular manifestations presented in moderate and severe hypersensitivity reactions<sup>[13,16]</sup>.

Recent research revealed that iodine is the initiating factor in immediate and delayed sensitivity reactions to iodinated CM<sup>[17]</sup>. Consequently, hyper-osmolar contrast agent use has been largely replaced in clinical imaging practices, over last two decades, with worldwide shift towards their non-ionic counterparts (whether; iso- or low-osmolar CM) thanks to improved safety profiles of these agents<sup>[18]</sup>.

Similarly, recent researches emphasized that immediate and moderate hypersensitivity reactions to GBCA may occur with high incidence in females, patients with history of allergies and previous reactions to CM<sup>[6]</sup>. Notably, severe hypersensitivity reactions to GBCA were higher for abdominal examinations rather than brain and spines<sup>[6]</sup>. Although an Ig-E mediated mechanism was suggested, the exact mechanism hasn't been elucidated. Interestingly, these hypersensitivity reactions seem to vary between various GBCA in different studies with no solid evidence whether it depends on the specific characteristics of gadolinium-based structure or not, at least for the GBCA immediate reactions<sup>[7,19,20]</sup>. On the contrary, delayed CM hypersensitivity reactions are thought to be T-cell mediated<sup>[10,14]</sup>.

## SERUM CREATININE SCREENING BEFORE CM EXAMINATIONS

Based on the safety profile of CM in clinical use nowadays, adequate screening questions as mentioned earlier, mitigates the need to have recent serum creatinine level done in normal average adults in most radiology practices<sup>[2,5,10,21]</sup>. However, having a laboratory renal profile for fragile patients due to senility and/or chronic debilitating disorders is highly advisable, especially in elective examination. Many patient co-morbidities require intentional lookup of the patient's renal profile (Table 2).

Renal creatinine is the widely acceptable indicator for renal function. The agreed upon simple general practices are to administer CM in patients with creatinine  $\leq$  1.5 mg/dL, be cautious in patients with creatinine in the range of 1.6-2.0 mg/dL, and to avoid contrast in patients with creatinine  $>$  2.0 mg/dL<sup>[8,9]</sup>.

Other groups suggested relying on estimated glomerular filtration rate (eGFR) as reliable indicators of renal function in adults, as it consider age, gender and ethnic variations<sup>[22,23]</sup>. eGFRs between 30 and 60 mL/min per 1.73 m<sup>2</sup> requires precautions to be practiced to avoid contrast induced renal injuries and needs close post-procedural monitoring of renal functions<sup>[8,9,22,23]</sup>.

In emergency examinations requiring CM ad-mini-stration, reliance on urine dipstick check for creatinine

**Table 3 Common elective premedication protocols for high-risk patients to develop iodinated contrast medium hypersensitivity reactions**

Lasser protocol	Elective		Emergency IV protocols (in descending order of desirability)
		Greenberger protocol <sup>1</sup>	
Oral prednisone 50 mg at 13/7 and 1 h before contrast medium injection		Oral methylprednisolone 32 mg at 12 and 2 h before contrast medium injection +/-	Methylprednisolone sodium succinate 40 mg  OR  hydrocortisone sodium succinate 200 mg every 4 h till examination  + diphenhydramine 50 mg <i>IV</i> - 1 h
+ (oral/ <i>IM</i> or <i>IV</i> ) diphenhydramine 50 mg just 1 h before examination		+/- (oral/ <i>IM</i> or <i>IV</i> ) diphenhydramine 50 mg just 1 h before examination	No corticosteroids at all (not preferable)  Only diphenhydramine 50 mg <i>IV</i>

<sup>1</sup>*IV* hydrocortisone 200 mg may be a substitute for oral prednisone, if the patient cannot tolerate oral medication.

done in the emergency room was suggested as a predict for serum creatinine along with adequate history taking<sup>[24,25]</sup>. Although no consensus exists regarding serum creatinine and CM administration time window, a renal profile done within last 30 d is an acceptable recent documentation in general<sup>[9,26]</sup>. The authors recommend shorter time-intervals for high-risk groups, however.

Concerns about volume of used iodinated CM and the usage of absolute rather than the absolute and relative creatinine levels are on the rise, more recently, to avoid systematic inaccuracies in assessment of renal function and avoid contrast-induced nephropathy<sup>[27,28]</sup>.

## PRE-MEDICATIONS FOR PATIENTS AT RISK

Premedication before *IV* contrast administration is a well-known and widely practiced protocol that aims to reduce the incidence of mild to moderate adverse reactions to iodinated CM, primarily<sup>[29,30]</sup>. However, the possibility of severe reactions occurrence albeit rare is unaffected by premedication regimens<sup>[16]</sup>.

Corticosteroids are the critical component of any premedication regime. The use of antihistamine alone or as a supplement to corticosteroids is a customary practice<sup>[8,9]</sup>. The mechanism of action of both drug groups is still controversial yet they are thought to interfere with the mechanisms of antigen-antibody response and actions of the released mediators<sup>[31]</sup>. However, the sole use of antihistamines did not prove to be working alone in prevention of contrast-induced hypersensitivity reactions<sup>[32]</sup>. Two common elective premedication protocols, the Lasser<sup>[34]</sup> and the Greenberger<sup>[34]</sup> (Table 3), are widely implemented and supported by recognized bodies<sup>[8,9]</sup>.

## HYDRATION (EXTRACELLULAR VOLUME EXPANSION)

The osmolality of iodinated CM was postulated to cause

extracellular fluid shifts, leading to cell dehydration and increased intracellular fluid viscosity, which precipitates cellular dysfunction<sup>[35]</sup>.

Volume expansion appears to be an amenable effective strategy to obviate contrast induced nephropathy (CIN). A practical hydration regime has to be initiated before and be continued for several hours after CM administration<sup>[36]</sup>. Various hydrations regimens either *via* oral and/or *IV* administration of crystalline solutions are available including normal and half-strength saline's, sodium bicarbonates infusion, N-acetylcysteine and statins<sup>[37]</sup>. Yet the privileges of one over another have not been effectively established; thanks to limited studies done in patients receiving *IV* CM for diagnostic purposes<sup>[36,37]</sup>.

## ADVERSE REACTIONS TO CM

CM adverse reactions are usually grouped according to their emergence and necessity for intervention into: (1) acute; happening during or within the 1<sup>st</sup> hour following injection; (2) late, presenting up to 1 week thereafter; and (3) very late group that surfaces weeks to months following contrast administration. However; for easy academic deliberation, we will consider it under two main categories, the (1) immediate (acute) adverse reactions; occurring up to one hour from injection; and the (2) non-immediate (delayed) reactions; occurring later on. Furthermore, for the increased awareness by renal side effects of different CM these will be sub-classified into renal and non-renal reactions.

## IMMEDIATE NON-RENAL ADVERSE REACTIONS TO CM

From practical point of view we will describe it as mild, moderate and severe reactions. Table 4 shows the immediate non-renal adverse reactions and their common manifestations as well as the general guidelines that every radiologist and/or medical staff dealing with CM reactions has to be oriented with.

In general, the majority of reactions to CM are mild in

**Table 4 Severity scale, signs, symptoms and management options of adverse reactions to contrast media**

Category of reaction	Symptoms	Treatment
Mild (self-limited without evidence of progression)	Hives, rashes and sweats Nasal symptoms Nausea, vomiting Pallor Cough Flushing Warmth Chills Headache and/or Dizziness Self limited anxiety	Patient reassurance usually suffices in some cases Close observation till resolution of symptoms May require symptomatic treatment in some cases
Moderate (signs and symptoms are more pronounced)	Generalized or diffuse erythema Tachycardia/bradycardia Bronchospasm, wheezing and/or dyspnea Hypo- or hyper-tension Voice hoarseness	Requires prompt treatment Requires close, careful observation for possible progression to a life-threatening event
Severe (sign and symptoms are often life-threatening)	Laryngeal edema (severe or rapidly progressing) Convulsions Profound hypotension Unresponsiveness Clinically manifest arrhythmias Cardiopulmonary arrest	Requires hospitalization and aggressive treatment by emergency teams

form of hives and nausea<sup>[5-7]</sup> and occurs within the first minutes following CM administration while severe and potentially life-threatening reactions to intravascular CM occur within 20 min after contrast administration<sup>[5,6,11,19]</sup>. It is recommended to keep patients under observation for 20-30 min in the radiology department after contrast medium injection<sup>[8,9]</sup>. This is of special consideration for the pediatrics population who can't verbally communicate. Mild reactions may require no more than observation, patient reassurance and/or a dose of an antihistaminic. In moderate to severe adverse reactions more therapeutic interventions will be implemented.

Every radiology practice has to be equipped with a general emergency cart loaded with up to date medications and instrumentations used in dealing with CM-induced reactions<sup>[8-10]</sup>. A cooperative plane with concerned emergency teams should be put into effect in hospitals to deal with severe reactions to CM.

### BREAKTHROUGH REACTION

A breakthrough reaction refers to a reaction that occurs after iodinated CM injection in patients who have already been intentionally pre-medicated to prevent CM sensitivity reaction<sup>[31]</sup>. So, they are patients who are principally labeled as being at high risk for a reaction. Severity of reaction is more or less similar to those of the initial reaction and needs likewise treatment. Practically, these patients should be advised that they are likely to be at increased risk for more severe reactions if iodinated contrast material is administered in the future. Furthermore, radiologists have to recommend other

alternative safe imaging modalities to help with their diagnoses.

### IMMEDIATE RENAL ADVERSE REACTIONS TO CM

Iodinated CM may cause disturbed renal functions known as contrast induced-acute kidney injury (CI-AKI), that is commonly defined as "abrupt deterioration in kidney function, manifested by an increase in serum creatinine level with or without reduced urine output"<sup>[38]</sup>. There are more specific diagnostic criteria for diagnosing (CI-AKI) delineated by the consensus gentium of concerned major concerned bodies (Table 5)<sup>[39]</sup>. Dehydrated, debilitated and high-risk chronic illness fragile patients, especially the diabetics, are more prone to develop CI-AKI<sup>[22,40-42]</sup>. CI-AKI is likely to be the result of burden of coexistent morbidity rather than the CM itself. Moreover, this depends on the base line renal profile<sup>[22,42,43]</sup>. Furthermore, it was noticed that CI-AKI is more likely to develop in patients undergoing intra-arterial use of contrast above the level of renal arteries more than in patients undergoing IV administration of the CM<sup>[41]</sup>.

### EXTRAVASATION

Extravasation refers to the escape of contrast material from the vascular lumen with infiltration of the interstitial tissue around injection site during injection. It is reported to be less than 1% and is not directly correlated with injection<sup>[44]</sup>. The physician has to promptly recognize and evaluate it to reduce the chance and severity of injury.

**Table 5 The criteria for diagnosing contrast induced-acute kidney injury**

Absolute serum creatinine increase of greater than or equal to 3.0 mg/dL (> 26.4 μmol/L)
An increase in the percentage of serum creatinine of greater than or equal to 50%
Urine output reduced to less than or equal to 0.5 mL/kg per hour for at least 6 h

**Table 6 European medicines agency nephrogenic systemic fibrosis-risk stratification categorization of gadolinium-based contrast agent**

GBCA NSF-risk class	Scientific (generic) name
Highest risk of NSF	Gadodiamide (Omniscan®)
	Gadopentetate dimeglumine (Magnevist®)
	Gadoversetamide (Optimark®)
Intermediate risk of NSF	Gadobenedate dimeglumine (Multihance®)
	Gadofosveset trisodium (Vasovist®, Ablavar®)
	Gadoxetate disodium (Primovist®, Eovist®)
Lowest risk of NSF	Gadobutrol (Gadovist®)
	Gadoterate meglumine (Dotarem®)
	Gadoteridol (Prohance®)

NSF: Nephrogenic systemic fibrosis; GBCA: Gadolinium-based contrast agent.

The staff in charge of CM injections should: (1) check the adequacy of vascular access; (2) adjust injection rate; (3) counsel the patient to report any unpleasant sensations at the injection site; and (4) monitor the injection site during and/or following the procedure.

If extravasation commences the injection should be withheld, assessment is done. Small and limited extravasations are self limited and just need monitoring, reassurance, hot and cold foment. Large injurious extravasations may require surgical intervention<sup>[45]</sup>.

## DELAYED NON-RENAL ADVERSE REACTIONS TO CM

Delayed contrast hypersensitivity is defined as a reaction that occurs 1 h to 1 wk following iodinated contrast administration. They are usually limited to skin rashes and occasionally mild and self limited. Originally, these reactions were reported to be associated with the non-ionic iso-osmolar iodinated CM<sup>[8,9]</sup>. However, recent reports addressed its occurrence following GBCA<sup>[11,19]</sup>.

### *Iodine-provoked thyroid dysfunction*

Iodinated CM have a free iodine content that is greatly higher than average daily human needs<sup>[46]</sup>. In general, it is contraindicated to administer iodine based CM intravascularly to patients at risk of thyrotoxicosis<sup>[2,9]</sup>.

Iodine-provoked thyroid dysfunction is a self-limited, relatively rare entity of transient altered thyroid hormones in the blood in response to high load of free iodine following intravenous administration of iodinated CM (disrupted auto-regulation)<sup>[46,47]</sup>. Subjects with normal

thyroid function are not at risk<sup>[47,48]</sup>. The problem is for patients with hyperthyroid states, *e.g.*, thyroid autonomy and Grave's disease who become deprived of thyroid hormones and need treatment adjustments. Theoretically speaking; long term suppression may end with hypothyroidism<sup>[46]</sup>.

Another caveat is patients planned for radio-active iodine scanning. In this population, the use of iodinated contrast agents has to be postponed after planned radioactive iodine imaging or therapy. Excess free iodine following IV administration of iodinated CM will saturate its receptors and result in sub-optimal or non-diagnostic studies and/or management of their disease<sup>[2]</sup>. A noteworthy point to mention here, is that iodinated CM used during <sup>18</sup>FDG-PET/CT do not have a dumping affect on the clinical assessment of these studies<sup>[49,50]</sup>.

Reports about iodine-provoked thyroid dysfunction following non-vascular uses have emerged recently and the issue has to be monitored by radiologists<sup>[51-53]</sup>.

## DELAYED RENAL ADVERSE REACTIONS TO CM (NEPHROGENIC SYSTEMIC FIBROSIS)

Actually, all iodinated CM have a nephrotoxic potential yet variable potentialities exist for GBCA<sup>[10,11,19]</sup>. Table 6 shows the popular classification of commercially available GBCA by European Medicines Agency EMA<sup>[54]</sup>.

Nephrogenic systemic fibrosis (NSF) is a serious progressive clinico-pathologic entity that may progress to be fatal. It has no associated imaging findings. NSF came into attention more than a decade earlier and has been described to develop in patients with compromised renal functions<sup>[55-57]</sup>. Clinically, it is a diagnosis of exclusion that can be suspected in patients showing variable skin rashes up to subcutaneous scleroderma-like plaques as well as variable systemic manifestations who received a GBCA<sup>[57,58]</sup>. However, these should be coupled with histological findings<sup>[58]</sup>. Although its pathogenesis has not been agreed upon, postulations assumed that weak stability of gadolinium chelates leads to its free dissociation in tissues and incite a fibrotic response in different body tissue. Association with linear; more than the macro-cyclic; formulas of GBCA is supportive for these assumptions<sup>[59,60]</sup>.

## POPULATIONS WITH SPECIAL CONSIDERATIONS

### *Patients liable to and/or actually have renal compromise*

It is of utmost importance for radiologists to identify patients with renal compromise in advance using same screening tips for identifying high risk groups, discussed in earlier section (Table 1). So radiologists can adhere to some precious strategies for safe clinical practice of CM to reduce risk for NSF (Table 7).

The use of renal protective agents such as N-acetylcysteine, sodium bicarbonate, diuretics, and theophylline is

**Table 7 Strategies for safe clinical practice of contrast media to reduce risk for renal complications in patients with renal problems**

Patients with SCr $\geq$ 2 g/dL and/or eGFR $\leq$ 60 mL/min per 1.73 m <sup>2</sup>	Withhold contrast whenever possible and use alternative imaging modalities if feasible Adequate hydration
Patients with end-stage renal disease who still produce urine	Consider alternative diagnostic study if feasible Avoid use of CM whenever possible Use lowest possible dose of contrast Use intermediate to low osmolar and/or low risk GBCA followed by prompt dialysis if the patient is already undergoing dialysis
Patients with end-stage renal disease who are anuric	Can receive routine volumes of intravenous contrast material without risk for further renal damage or the need for urgent dialysis

GBCA: Gadolinium-based contrast agent; CM: Contrast media; eGFR: Estimated glomerular filtration rate.

**Table 8 Practical guidelines for safe contrast media-metformin interaction**

Renal function (eGFR-indexed)	Action
Patients with normal renal function (eGFR $\geq$ 60 mL/min per 1.73 m <sup>2</sup> )	No need to withhold metformin
Patients with compromised renal function (eGFR $\geq$ 30 but $\leq$ 60 mL/min per 1.73 m <sup>2</sup> )	Withhold metformin for 48 h Re-institution after renal function monitoring
Patients with compromised renal function (eGFR $<$ 30 mL/min per 1.73 m <sup>2</sup> )	Have not to be on metformin Consult nephrologist

eGFR: Estimated glomerular filtration rate.

debatable and has not proven great benefits<sup>[36]</sup>. The previous recommendations of hemodialysis in patients at high risk for CM-associated complications are no longer sound and consulting a nephrologist is a wisdom practice<sup>[61]</sup>.

### METFORMIN

Metformin is an oral anti-hyperglycemic agent, commonly, used to treat patients with non-insulin-dependent diabetes mellitus. Metformin is excreted unchanged in the urine. However, in the presence of renal failure, either pre-existing or induced by iodinated contrast medium, metformin may potentially accumulate in sufficient amounts to cause lactic acidosis. Hence, radiologists have to cautiously approach those patients for safe practices considering the potentiality for contrast-induced renal injury with subsequent metformin use co-morbidity (Table 8)<sup>[2,8,9]</sup>. For GBCA, there is no necessity to discontinue metformin before examinations, however<sup>[9]</sup>.

### PREGNANT AND NURSING WOMEN

Although iodinated contrast agents and gadolinium

cross the placenta in little traces reaching the fetus, no definite gene mutation or teratogenic effects have been reported in human<sup>[62,63]</sup>. The large scientific bodies in radiology<sup>[8,9]</sup> recommend that, no contrast should be administered to the pregnant mother unless there is prudent need to intervene to save both mother and baby, based on these contrast-enhanced studies. Furthermore, post-natal assessment of neonatal thyroid function has to be carried if the administered CM was iodine-based<sup>[53,64]</sup> while this is not of clinical utility for the GBCA<sup>[8,9,63]</sup>.

Small traces of iodinated contrast material or GBCA are excreted in breast milk and absorbed by the infant with no reports of fetal reactions to the best of author's knowledge. So, breast feeding abstinence following contrast studies of nursing women is not recommended<sup>[8,9,26]</sup>.

### PEDIATRICS

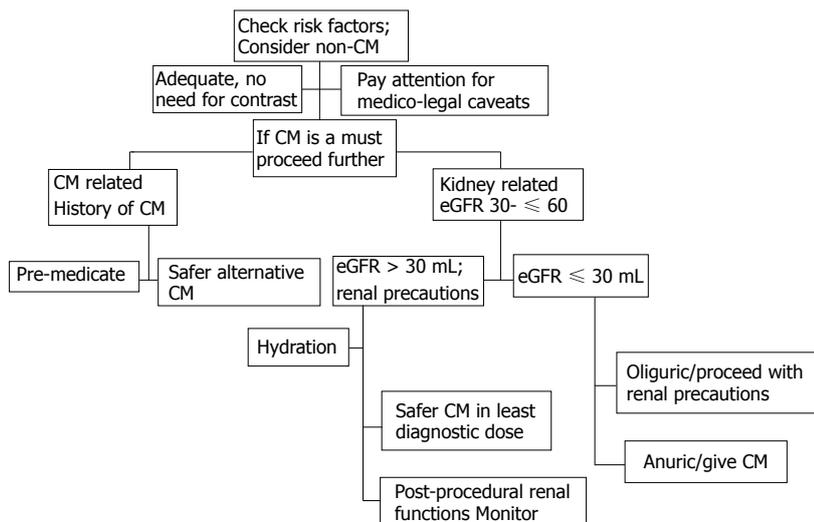
Due to limited number of studies, estimating the incidence of reactions to CM in children is difficult. Special considerations have to be weighted when dealing with infants and young children. These include: Fluid shifts in neonates, low weights, immaturity of their renal function, lower (eGFR), fragile vascular access and lack of communicability. Most CM reactions in children are mild and in the form of skin and respiratory reactions. Warming of iodinated CM before administration to children is recommended to increase their viscosity and diminish rates of contrast reaction<sup>[65,66]</sup>. Other recommendations may include, use of low-osmolality contrast agents, diminishing the volume of contrast given, avoid nephrotoxic drugs and adequate hydration of the patient<sup>[67]</sup>.

GCBA reactions are rare in children and exclusively presented in children with pre-existing renal problems<sup>[68]</sup>. However, GBCAs use should be limited in children and only used when necessary<sup>[9]</sup>. Recent reports recommended the use of gadobenate dimeglumine (Multihance) in pediatrics of different ages<sup>[69]</sup>.

### CM: MEDICO-LEGAL CAVEATS

Informed consent is defined as "a process of a patient-physician communication that results in the patient's authorization or agreement to undergo a specific medical intervention"<sup>[70]</sup>. The aim of informed consent is to gather relevant information that makes the procedure both safe and comfortable as possible<sup>[26]</sup>.

With increased daily implementation of different clinical imaging modalities worldwide, obtaining an informed consent remains a practical caveat as it is not possible to achieve its requirements for every running contrast-enhanced imaging procedures<sup>[71]</sup>. Practically, this is compromised by patient's unfamiliarity with the invisible nature of radiation, its measurements and the probability of its stochastic effects compared to orientation with incisions and intubations for example<sup>[72]</sup>. Moreover, informed consent timing, work list scheduling and radiologists' discomfort, about discussing CM complications



**Figure 1** Procedural infographic display for safe clinical practice use of iodinated and gadolinium-based contrast agent for IV use in clinical imaging. CM: Contrast media; eGFR: Estimated glomerular filtration rate.

with their patients are added limitations for the classic informed consent process<sup>[73]</sup>. After all, the patient-radiologist relationship is brief and episodic, especially for the outpatients basis<sup>[72,73]</sup>.

Based on the aforementioned highlights and the documented evidences that CM are largely safe drugs, a ready to sign informed consent form, by the patient or his/her guardian, is a customary practice worldwide in most radiology practices<sup>[26,73]</sup>. Previous reports emphasized that adoption of adequate interactive verbal communication, along with providing multi-media approaches, *e.g.*, on-site videos, leaflets, educational seminars, *etc.*, explaining the benefits of CM use, the rarity of their hypersensitivity reactions, the propensity of these reactions to be mild and transient, and the identifications of the populations at risk for developing it, can effectively relieve the patient's apprehensions and confusions for elective diagnostic imaging as well as interventional procedures requiring the administration of CM<sup>[74-76]</sup>.

The authors believe that conducting those steps along with providing an easy to tick, short targeted questionnaire fulfills the aim of informed consent, by identifying high-risk populations to develop CM reactions, and make the process of gaining it is a time-effective and easy routine. Undoubtedly, these routine practices relieve the patient's anxiety and mitigate an important provoking element thought to be involved in developing reactions to CM<sup>[77]</sup>.

Justification for the use of CM based on clinical concerns is the sole responsibility of the radiologist in charge based on regional laws, institutional and departmental policies<sup>[8,9]</sup>.

Another medico-legal caveat is the off-label contrast media (OLCM) which are defined as CM that are used in otherwise originally tested, indicated and licensed purposes, *e.g.*, CT and/or MR angiographic, cardiac and arthrographic procedures<sup>[73,78]</sup>. Although, these applications are proved; by recognized scientific bodies<sup>[8,9]</sup>

as well as scientifically-based well conducted large population and multicenter studies<sup>[7]</sup>; to be clinically beneficial and are widely used since decades, the use of CM for these examinations remains outside legal boundaries<sup>[78,79]</sup>. This imparts medico-legal responsibility to the radiologist in charge to divulge exhaustive information to patients and get a documented informed consent from patients before proceeding into such procedures. Shortly, most scientific societies and regulatory bureaus ascertain that radiologists using CM for an off-label indication should judge his/her use based on sound scientific medical evidences and should maintain a record of the products used and their effects<sup>[80]</sup>.

Lastly, a simple applicable working safety practice hierarchical info-graph for administrating radiographic and MR CM is suggested by the authors (Figure 1).

## CONCLUSION

In conclusion, radiologists as well as faculty staffs dealing with radiographic and MR CM have to be well oriented with the potential CM hypersensitivity reactions, high-risk groups liable to develop it and their early recognition. They have to be ready to implement prompt and effective management plan to deal with these reactions should they arise. Faculty staff dealing with radiographic and MR contrast administrations have to exercise strategies to prevent potential contrast-induced acute and delayed renal injuries and pay attention to the pregnant and nursing women, pediatrics, diabetics, as well as other fragile populations for optimized patient safety. Moreover, radiologists should be oriented with the medico-legal issues related to use of CM and play pivotal role in patient learning and assurance about CM safety. These will pay dividends as improved patient safety as well as safe radiology practices and working environment.

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