



# Updated guidelines for intravenous contrast use for CT and MRI

Kevin Huynh<sup>1</sup> · Arthur H. Baghdanian<sup>2</sup> · Armonde A. Baghdanian<sup>2</sup> · Derek S. Sun<sup>1</sup> · K. Pallav Kolli<sup>1</sup> · Ronald J. Zagoria<sup>1</sup>

Received: 1 November 2019 / Accepted: 3 January 2020  
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## Abstract

Intravenous (IV) contrast material is used extensively for CT and MRI scans done in emergency departments (ED). Its use is essential to make many critical diagnoses in ED patients. While adverse reactions can occur, newer research has added to our knowledge of IV contrast media tolerance and safety leading to improved and more liberal guidelines for intravenous contrast use. The updated information described in this review article indicates how intravenous contrast can be used safely in more patients, more expeditiously and with fewer precautions than with prior guidelines. This review article explains the basis for the new recommendations for intravenous contrast material use and describes indicated precautions and preparations to avoid adverse reactions for iodinated agents used for CT and gadolinium agents for MRI.

**Keywords** Contrast material · Emergency radiology · CT · MRI · Gadolinium

## Introduction

Since the introduction of the first commercial computed tomography (CT) scanner in the 1970s and MRI in the 1980s, the utilization of imaging has increased significantly nationwide [1, 2]. Over 70 million CT scans and 35 million MRI scans are performed in the USA annually [3]. The use of intravenous (IV) contrast in many of these scans is essential for accurate and definitive diagnosis of many disorders, and withholding IV contrast often diminishes the scan value for disease diagnosis. An estimated 75 million doses of IV contrast are given annually [4]. Modern contrast agents are safe for use with a low incidence of adverse side effects. Retrospective studies demonstrate an incidence of serious adverse effects in less than 1% of patients exposed to these various IV contrast agents [5–7]. In the emergency department (ED) population, there is a threefold increase in the utilization of CT imaging over the last two decades [8]. Recent research has led to the liberalization of some

IV contrast use guidelines, which will be discussed in this article. This review aims to provide evidence-based guidelines for screening patients before administering contrast, describing types of adverse contrast reactions, updating premedication regimens, and explaining strategies for the management and treatment of adverse reactions.

## Safety concerns surrounding IV iodinated contrast use

The incidence of post-contrast acute kidney injury (AKI) in the general population has been reported to be between 2 and 30% in patients. Risk factors cited to increase the risk of post-contrast AKI include chronic kidney disease, cardiovascular disease, and diabetes mellitus [9]. In the 1950s, there arose concern about IV iodinated contrast causing decreased kidney function [10, 11]. Initial studies suggested a strong causal association between iodinated IV contrast use and AKI. AKI, as defined by KDIGO criteria, is an (1) increase in serum creatinine (SCr) by  $\geq 0.3$  mg/dL within 48 h, (2) a  $\geq 1.5$ -fold increase in SCr, or (3) oliguria ( $< 0.5$  mL/kg/h for 6 h) [12]. Patients can develop AKI due to numerous different etiologies with a range of varying clinical presentations indistinguishable based on cause, but often attributed to contrast-induced nephropathy (CIN).

The initial studies associating IV contrast use with kidney injury had serious limitations; they lacked adequate control

✉ K. Pallav Kolli  
Kanti.Kolli@ucsf.edu

<sup>1</sup> Department of Radiology and Biomedical Imaging, University of California San Francisco, 505 Parnassus Ave, San Francisco, CA 94143, USA

<sup>2</sup> Department of Radiology, University of Southern California, 1975 Zonal Ave, Los Angeles, CA 90033, USA

groups, patients received older ionic high-osmolar contrast agents which are no longer in use, and there were varying definitions of CIN. More recent studies have found little to no correlation between AKI and newer low-osmolarity IV contrast [13–19]. Newhouse et al. evaluated 32,161 hospitalized patients who had their serum creatinine recorded for five consecutive days with no administration of iodinated contrast during their length of hospital stay. The authors found that the rates of serum creatinine elevation in hospitalized patients were similar to the incidence of contrast nephropathy in previously published studies [20]. These findings suggested that confounding factors other than iodinated contrast administration can lead to elevated serum creatinine. Early studies evaluating iodinated contrast use and CIN were also plagued by numerous confounders that led experts to question whether IV iodinated contrast was truly causing kidney injury. Studies that compared rates of adverse events in patients who underwent only contrast-enhanced CT vs cardiac catheterization showed 0% CIN and 0% mortality in patients undergoing contrast-enhanced CT vs 37% CIN and 22% mortality in patients undergoing cardiac catheterization [21, 22]. Many of the studies that evaluated CIN within the last two decades were not randomized and were vulnerable to selection bias. Recent studies utilized propensity score adjustment to correct for selection bias [23–27]. Davenport et al. demonstrated that after one-to-one propensity matching, an  $\text{eGFR} \geq 60 \text{ mL/min/1.73 m}^2$  was not associated with an increased risk of developing post-contrast AKI (OR 1.00; 95% CI 0.86–1.16) whereas patients with pre-existing renal dysfunction with  $\text{eGFR} < 30 \text{ mL/min/1.73 cm}^2$  had a significantly increased chance of developing post-CT AKI (OR 2.96; 95% CI 1.22–7.17) [23]. Similarly, McDonald et al. also utilized propensity scoring of 12,508 matched patients and compared subgroups of patients with an IV contrast-enhanced study to matched patients who only received a non-contrast CT study and found no statistically significant difference in the rate of AKI in any  $\text{eGFR}$  subgroup analyzed ( $\text{eGFR} < 30$ , 30–60, 60–90,  $> 90 \text{ mL/min/1.73 m}^2$ ). Notably, this study differed from the study by Davenport et al. in that they did not find an increased risk of developing AKI even in patients with  $\text{eGFR} < 30 \text{ mL/min/1.73 cm}^2$ . Currently, the evidence demonstrates that patients with an  $\text{eGFR} > 30$  do not have an increased risk of developing post-contrast AKI [23, 28]. It remains unclear whether patients with an  $\text{eGFR} < 30$  are at an increased risk of developing post-contrast AKI, but based on recent studies [23, 28], the incidence of AKI is lower (0–10%) than previously understood. As such, some institutions take a conservative approach and caution against the routine use of iodinated IV contrast in patients with an  $\text{eGFR} < 30$ . These studies that utilized propensity weighted scoring also identified the primary risk factors for CIN. Unsurprisingly, these risk factors primarily revolve around impaired renal function. Major risk factors that have been independently associated with CIN identified

include older age, low  $\text{eGFR}$ , history of renal disease, diabetes, and hypertension [24, 29].

Two main strategies are employed to reduce the incidence of post-contrast acute kidney injury in “at-risk” patients. The first strategy is to avoid contrast entirely if contrast will not influence clinical management or if a different imaging modality can also answer the clinical question. Second, peri-exposure volume expansion can reduce rates of post-contrast acute kidney injury [30–33]. Propensity matched studies have not specifically examined hypovolemia or dehydration as a major risk factor for contrast-associated kidney injury. However, there is a theoretical concern that low intravascular volume may lead to decreased  $\text{eGFR}$  and increased tubular contrast transit time, in turn increasing the risk of post-contrast acute kidney injury. The optimal volume, rate, route, or type of crystalloid for volume expansion is not known at this time. One major randomized control demonstrated that isotonic crystalloid is preferred over half-isotonic crystalloid [30]. Volume expansion with bicarbonate has been proposed as potential prophylaxis to prevent contrast-associated kidney injury based on favorable animal model studies. Several trials have shown that volume expansion with bicarbonate solution reduced rates of CIN compared to normal saline alone [34, 35]. However, subsequent studies have had conflicting conclusions with the use of bicarbonate associated with increased rates of CIN or demonstrating equivocal results to saline [36, 37]. Further confirmatory studies are needed and in the setting of conflicting data, bicarbonate is not recommended for prophylactic volume expansion regimens. A commonly used and expeditious hydration regimen is summarized in Table 1

## Screening prior to administration of iodinated contrast

Although the risks of using iodinated contrast are small, screening patients prior to IV administration is still recommended to identify those patients at highest risk for an adverse event (Tables 2 and 3). The specific goals of screening are to identify patients with renal impairment and to identify patients with prior adverse side effects from IV iodinated contrast administration. Patients should be assessed using a standardized “Patient Screening Form” to indicate relevant medical history and history of previous reactions to iodinated contrast (Table 2). Routine laboratory assessment of renal function for all patients prior to administration of contrast is not recommended. In a study of 2034 patients who underwent CT with IV contrast, only 3.2% (66/2034) of patients had elevated serum creatinine at the time of testing [40]. Only 2/66 (3% of patients with abnormal serum creatinine, 0.1% of all patients) had no identifiable risk factors for pre-existing abnormal renal function. Therefore, careful pre-scan assessment of a patient’s clinical history for potential risk factors for pre-

**Table 1** Recommendations for iodinated contrast administration and hydration [38, 39]

| eGFR (mL/min/1.73 m <sup>2</sup> ) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ≥ 30                               | <i>Low risk.</i> Limited evidence suggesting intravenous iodinated contrast material is an independent risk factor for AKI in patients with eGFR ≥ 30 mL/min/1.73 m <sup>2</sup> . No hydration required.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| < 30                               | <i>Higher risk.</i> This population of patients has the greatest risk for post-contrast acute kidney injury after administration of intravenous iodinated contrast. <i>Contrast is not recommended</i> unless the patient is on dialysis and anuric, or if contrast is considered diagnostically essential. Weigh the benefits of contrast versus potential harms of kidney injury. Pre-procedural prophylaxis with intravenous volume expansion therapy is recommended.<br><br>The optimal IV volume expansion protocol is unknown and ideally should be tailored to the patient's volume status and medical conditions. Suggested protocols:<br>•Inpatients—0.9% normal saline at 100 mL/h IV beginning 6–12 h prior to contrast administration and continuing 4–12 h afterwards<br>•Outpatients—0.9% normal saline 500 mL IV bolus prior to contrast administration. Consider post-exposure oral hydration (1 cup of water per hour for 8 h) unless medically contraindicated. |

existing renal disease can be sufficient to reduce unnecessary laboratory tests for patients that are not at risk. In patients who have a known history of renal impairment, a recent creatinine or eGFR within the past 6 weeks for outpatients or last 7 days for inpatients is considered appropriate for evaluation of renal function at the authors' institution. If a recent creatinine or eGFR is unavailable, patients are assessed with four key screening questions as listed in Table 3 to determine if eGFR testing is needed.

**Intravenous iodinated contrast administration in patients with renal failure requiring dialysis**

The use of iodinated contrast in patients receiving dialysis is generally considered to be safe. However, practicing clinicians should be mindful of using IV contrast in the following circumstances: in the patient who is still able to produce urine,

where dialysis is being performed with the expectation of renal recovery, and in patients sensitive to volume overload. Administration of an iodinated IV contrast in these settings may risk further injury, decrease the chance to reverse renal impairment, or worsen underlying chronic disease. In the setting of late-stage CKD where the patient still produces a small amount of urine, there is a theoretical concern that remaining renal function may be jeopardized by administration of iodinated IV contrast [41]. IV contrast may further exacerbate declining renal function and increase the frequency of dialysis. In patients sensitive to volume overload (e.g., congestive heart failure), administration of IV contrast may worsen intravascular volume status leading to potential decompensation and worsening of their underlying chronic cardiac disease [42]. Although hemodialysis (HD) can effectively eliminate iodinated IV contrast from the bloodstream [43] and systemic circulation, it is not effective for the reduction of CIN [44, 45]. In one study, 113 patients with stable renal failure who underwent angiographic interventions requiring IV contrast were randomly assigned to receive either 1 mL/kg/h of IV saline for 12 h post-contrast or were assigned to receive post-contrast HD. The rate of CIN, defined by the investigators as an increase in SCr by > 1.5 mg/dL or > 50% rise above measured baseline, did not significantly differ between the two groups [46]. Cruz et al. performed a meta-analysis of nine randomized controlled studies and 2 nonrandomized trials of 1010 patients who received renal replacement therapy (HD or hemofiltration). The investigators found that renal replacement therapy was not associated with a significant decrease in rates of CIN (RR 1.02; 95% CI 0.52–1.93). When the analysis was limited to only patients receiving HD, the investigators found that HD was paradoxically associated with an increased risk of CIN (RR1.61; 95% CI 1.13–2.28) but had no

**Table 2** Pre-iodinated-contrast questionnaire to determine risk of contrast-associated adverse events and need for pre-contrast intervention

|                                                                                                      |
|------------------------------------------------------------------------------------------------------|
| Screening form questions:                                                                            |
| 1. Have you ever had a previous reaction to intravenous contrast?                                    |
| 2. Have you ever had a life-threatening allergic reaction (both medications and food)?               |
| For women of child-bearing age:                                                                      |
| 3. Is there a possibility that you may be pregnant?                                                  |
| 4. Are you breastfeeding?                                                                            |
| If answered yes to any of the questions above, consultation with supervising radiologist recommended |

**Table 3** Screening questions for patients without recent renal function studies to assess for need for further laboratory screening

Screening questions to determine need for further renal studies

1. What is your current age?
  2. Do you have diabetes?
  3. Do you have high blood pressure requiring medication?
  4. Do you have ANY problems with your kidneys (i.e., transplant, single kidney, renal cancer, dialysis, kidney surgery)?
- If < 60 years old and answered NO to questions 2–4, IV contrast can be administered without laboratory workup for renal function.
  - If > 60 years old and/or answered YES to any of the questions, assess renal function with laboratory workup prior to administering contrast.

significant effect on the need for permanent dialysis or progression to renal disease [47]. Thus, IV contrast use in patients on chronic HD who make no urine is safe without special precautions. HD patients who receive IV contrast do not require routine post-procedural dialysis. However, dialysis itself does not automatically qualify patients to receive IV contrast without evaluation of renal status and other comorbidities. Nephrology consultation should be considered for patients with acute renal failure and other HD patients with complex renal disease before using iodinated IV contrast if its use is determined to be required for the diagnosis of a critical illness.

### Iodinated IV contrast administration in patients receiving metformin

The management of metformin in the setting of IV iodinated contrast use has been intensely debated with different professional societies having varying recommendations [48, 49]. Metformin gained FDA approval in 1995 and is now one of the most commonly used oral-glycemic agents in the USA. It is considered to be one of the safest medications for the management of diabetes. Metformin is renally eliminated and accumulation of metformin has been associated with lactic acidosis (LA) [50]. This association with lactic acidosis has been controversial. A Cochrane review of 347 controlled trials with a cumulative 70,490 patient-years on metformin vs 55,451 patient-years in the non-metformin group demonstrated no evidence that metformin was associated with an increased risk of LA [51]. However, critics note that these studies are limited in that they excluded patients with CKD [52, 53]. Specifically, the Cochrane review contained 191 studies that excluded CKD patients [51]. The data regarding metformin and LA in patients with impaired renal function is mixed. Eppenga et al. conducted a population cohort study that followed 223,968 patients on metformin and 34,571 diabetic patients not on metformin for 4.3 years and 4.9 years respectively. Rates of LA were significantly higher in patients with an eGFR < 60 (adjusted HR 6.37; 95% CI 1.48–2.75) [54]. A more recent

cohort study by Lazarus et al. followed 75,413 patients on metformin with a median follow-up of 5.7 years found that risk of LA was increased only in patients with eGFR < 30 (adjusted HR 2.07; 95% CI 1.33–3.22) [55]. One limitation of the Eppenga et al. study was that it was unable to account for changes in eGFR over time which could be a confounder for the study. Lazarus et al. were able to account for changing GFR in their analysis and demonstrated that GFR is independently a strong risk factor for acidosis [55].

Metformin itself does not increase the risk of patients developing AKI. Bell et al. followed 25,148 diabetic patients for a total of 126,904 patient-years and analyzed whether metformin was associated with AKI incidence. They found that current metformin use was not independently associated with the onset of AKI (HR 0.94; 95% CI 0.87–1.02) and those who did develop AKI on metformin were associated with a higher survival rate at 28 days (HR 0.91; 95% CI 0.69–0.94) [56]. Because metformin is primarily excreted by the kidney, there is a theoretical risk that post-contrast acute kidney injury may precipitate lactic acidosis. Currently, there are no reports of LA from iodinated contrast in patients with eGFR > 30. Examination of rare cases of iodinated contrast and metformin-associated lactic acidosis has shown that nearly all cases occurred when patients were receiving metformin despite having one or more contraindications to the medication [57]. At this time, there is no evidence that supports discontinuing metformin prior to and after administering iodinated contrast if a patient has an eGFR ≥ 30 and has no evidence AKI. This is due to the fact that the vast majority of patients on metformin with an eGFR > 30 have no significant risk of developing LA [55]. Patients with a history of severe CKD (stage IV or V; eGFR < 30) or the presence of AKI should discontinue metformin prior to or at the time of the procedure. In this subgroup of patients, metformin should be held for 48 h after the procedure and restarted only after checking eGFR (Table 4).

**Table 4** Risk factors and clinical approach to using group III gadolinium agents

| Risk category       | Clinical features                                                                                                                                              | Approach                                                                                                                                                                                                                                                                  |
|---------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| High risk           | <ul style="list-style-type: none"> <li>• eGFR &lt; 30 or on dialysis</li> <li>• Acute kidney disease (decrease in eGFR ≥ 35% in less than 3 months)</li> </ul> | <ul style="list-style-type: none"> <li>• Group III agent not recommended</li> <li>• If needed, use lowest dose possible and consult with a radiologist</li> <li>• Obtain informed consent</li> <li>• Consider early hemodialysis if patient is on hemodialysis</li> </ul> |
| Low/negligible risk | <ul style="list-style-type: none"> <li>• eGFR &gt; 30</li> </ul>                                                                                               | <ul style="list-style-type: none"> <li>• Single dose appropriate</li> </ul>                                                                                                                                                                                               |

## Safety concerns surrounding gadolinium contrast use

Gadolinium is a rare earth metal and currently the primary contrast agent used in magnetic resonance imaging (MRI). Beginning in the 1980s, investigators looked into utilizing magnetic/paramagnetic reagents as contrast agents for MRI [58, 59]. By 1988, gadopentetate dimeglumine (Magnevist®) was the first commercially available MRI contrast agent to be used clinically [60]. Since then, numerous other gadolinium agents have gained regulatory approval and are used clinically. Gadolinium agents were historically believed to be remarkably safe: in a retrospective study of over 21,000 patients who received gadolinium, only 0.17% of patients had an adverse reaction [61]. At one point, it was suggested to use gadolinium in place of iodinated contrast in CT imaging because of its favorable side effect profile [62]. However, beginning in the early 2000s, a series of publications emerged that associated gadolinium contrast with nephrogenic systemic fibrosis (NSF). NSF is characterized by widespread fibrosis of the skin and internal organs that can become debilitating and potentially fatal. Cowper et al. first identified a scleromyxoedema-like disease in fifteen patients requiring dialysis in which he described increased fibroblast activity with deposition of collagen and mucin in the skin [63]. Multiple similar case reports emerged that also described cases of a similar multi-organ sclerosing disease in patients with end-stage renal disease on dialysis [64, 65]. Finally, in 2006, two independent papers identified gadolinium as the primary risk factor with the strongest association with NSF [66, 67]. The pathophysiology of how gadolinium causes NSF is not completely understood, but several proposed theories revolve around the buildup of gadolinium ions in soft tissues [68]. The prevailing theory is based on the dissociation of free gadolinium ions from the chelating agent it is bound to. This is based on different incidences of NSF between contrast agents [69]. The type of gadolinium chelating agent that binds the gadolinium ion varies between different types of gadolinium products. Gadolinium ions are bound either to a linear or macrocyclic chelating agent. In animal models, linear agents have been shown to dissociate more readily than macrocyclic agents [70]. Linear agents have an increased association with NSF whereas macrocyclic agents tend to have a better safety profile [69]. Macrocyclic agents chelate more strongly to gadolinium and have been rarely associated with NSF. In about 32 million administrations of Gadavist, a commonly used macrocyclic agent, only 2 cases were diagnosed with NSF [71].

The greatest risk factor for developing NSF is poor renal function. Patients with CKD stage 4 or 5 have an estimated 1.7% chance of developing NSF with linear agents [66, 72, 73]. Since the adoption of more stringent screening guidelines and decreased use of linear gadolinium contrast agents, the incidence of NSF has been close to zero [74].

With numerous IV gadolinium contrast agents available on the market, the American College of Radiology has produced a classification system that stratifies gadolinium agents based on their association with NSF (Table 5) [38]. Group I agents are composed of linear agents and have since fallen out of favor and are no longer recommended for use at many institutions given the high risk of developing NSF. In contrast, group II agents have shown to have a near-zero association with NSF even in high-risk patients. Therefore, routine screening and laboratory testing for renal failure are no longer required prior to the administration of group II agents (Table 5) [75–77]. Group III agents such as gadoxetic acid (Eovist®) are preferred for certain clinical indications where hepatobiliary excretion is needed. While group III agents are linear agents, there is limited data available regarding the association between these agents with NSF, with no unconfounded cases of NSF reported with use. However, given group III agents' structural composition and limited data, routine screening of eGFR is recommended prior to administration with recommendations for cautious use and informed consent when eGFR is  $< 30 \text{ mL/min/1.73 cm}^2$ .

The long-term effects of IV gadolinium outside of NSF are not well understood. Studies utilizing mass spectrometry have demonstrated the presence of gadolinium in histologic autopsy samples with a dose-dependent relationship [78]. However, other than NSF, no untoward clinical consequences have been associated with gadolinium retention despite millions of MRIs with gadolinium-based contrast agents over three decades [79]. Further research in this area with well-conducted prospective studies will be needed to better understand the long-term effects of IV gadolinium and its retention in tissue.

## Screening prior to administration of gadolinium contrast

If a patient presents with renal failure, the necessity of a group II agent should be confirmed by the attending radiologist. If a group II agent is used in a patient with end-stage renal failure on dialysis, some recommend that dialysis should be performed as soon as possible after contrast administration to minimize the systemic circulation time of the contrast. Group I agents are contraindicated in patients on dialysis. Group III agents such as gadoxetic acid (Eovist®) as described above are commonly used given their hepatobiliary excretion and ability to provide a post-contrast hepatobiliary phase. Serum testing for eGFR is recommended prior to giving a group III agent (Table 5). A history of acute kidney disease (decrease in eGFR of  $\geq 35\%$  within 3 months) may increase the risk of developing NSF with group III agents [12]. Patients with an eGFR  $< 30$  or with risk factors listed above are not recommended to receive group III gadolinium agents.

**Table 5** American College of Radiology classification of gadolinium contrast agents based on association with NSF [38]. Group I agents are associated with the highest number of NSF cases and are no longer recommended for use. Group II agents are associated with a small

number of NSF cases and do not require routine screening prior to administration. Agents in group III have limited data available regarding NSF risk and require informed consent when eGFR < 30

| Group | Agents                                                                                                                  | Recommendation                                                |
|-------|-------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|
| I     | Gadodiamide (Omniscan®)<br>Gadopentetate dimeglumine (Magnevist®)<br>Gadoversetamide (OptiMARK®)                        | Not recommended for use in patients with CKD                  |
| II    | Gadobenate dimeglumine (MultiHance®)<br>Gadoteridol (ProHance®)<br>Gadobutrol (Gadavist®)<br>Gadoterate acid (Dotarem®) | Screening not required prior to administration                |
| III   | Gadoxetic acid (Eovist®)                                                                                                | Screening recommended<br>If eGFR < 30 informed consent needed |

If a group III agent is determined necessary to use by the radiologist and the ordering clinician, informed consent is recommended when the patient's eGFR is less than < 30 mL/min/1.73 cm<sup>2</sup> (Table 5). In patients who regularly receive HD, as with the above recommendations for group II agents, early post-contrast HD should also be considered when administering group III gadolinium agents. Patients with an eGFR > 30 mL/min/1.73 cm<sup>2</sup> can safely be given a dose of a group III gadolinium agent (Table 4).

## IV contrast administration in patients who are breastfeeding

Few studies examine the safety of breastfeeding following the administration of IV iodinated contrast. Most studies are limited by small sample size, but results across different studies have been remarkably consistent. Numerous studies that examined the plasma half-life of IV iodinated contrast medium have shown almost complete clearance from bloodstream within 24 h in patients with normal renal function [80–82]. The amount of iodinated contrast that is excreted in breast milk within the first 24 h after receiving IV contrast is small. Studies regarding iodinated contrast have shown that less than 1% of iodinated contrast is excreted in breast milk [82]. There is minimal binding of contrast to breast milk proteins because iodinated contrast is non-ionized and highly water soluble [83].

Similar to iodinated contrast reagents, gadolinium is minimally excreted into breast milk. A study of 20 lactating women who were given IV gadolinium contrast had breastfeeding interrupted for 24 h while breast milk was serially collected during that time. The excreted dose after 24 h of collection was 0.04% (0.507 µmol) of their initial dose [81]. This is over 100 times less than the typical contrast dose that can be given intravenously to neonates [81]. Moreover, in fecal excretion

studies, only 0.08% of orally administered gadopentetate was actually absorbed [84]. Therefore, of the minuscule amount of contrast that is excreted in breast milk, only a fraction of that amount is subsequently absorbed. Breastfeeding following administration of iodinated and gadolinium IV contrast is considered safe. The decision to pump and dispose of breast milk produced within 24 h of either iodinated or gadolinium contrast agent injection is optional, given the extremely low risk of it causing any adverse side effect.

## Contrast administration in patients who are pregnant

Most of the studies on the potential teratogenicity of IV contrast agents are based on several animal studies. These animal studies have consistently demonstrated that iodinated contrast is not associated with teratogenic effects [85, 86]. Iodinated contrast has been theorized to potentially suppress fetal thyroid function through an influx of exogenous iodine. In a retrospective study of 115 pregnant patients with an average gestational age of 28 weeks, the authors identified patients who received iodinated contrast for CT-angiography for pulmonary embolism (PE) detection and compared them against pregnant patients who received radiotracer perfusion imaging only. Neonatal TSH levels at 5–8 days of life were compared between the two groups. No statistically significant difference was observed between the neonates of mothers who received iodinated contrast vs the neonates of mothers who did not [87]. A similar study evaluated 344 women with a mean gestational age of 27.8 weeks who received a one-time dose of low-osmolar iodinated contrast as part of PE rule out studies. The rate of abnormal T4 levels (as appropriate for gestational age) was found in 0 out of 343 newborns [88]. Both studies have shown that one-time iodinated contrast exposure was not associated with long-term thyroid abnormalities in neonates. It

is postulated that fetal protective mechanisms can adequately compensate for the transient acute rise in serum iodine [88]. Thus far, no studies have demonstrated clear harm to the fetus, and screening for pregnancy is not recommended prior to administration of iodinated IV contrast.

While gadolinium agents have not been associated with teratogenicity, they have been associated with several potential adverse events [89]. An analysis of 1,424,105 deliveries in Canada, with a rate of 3.97/1000 MRIs during pregnancy, found an increased risk of rheumatologic, inflammatory, or infiltrative skin conditions in mothers given gadolinium during pregnancy [90]. Gadolinium was also associated with an increased risk of stillbirth and neonatal death (HR 1.36; 95% CI 1.09–1.69). Because of the association with increased adverse fetal outcomes, gadolinium should be avoided in pregnant patients unless the clinical benefits outweigh the risks.

## IV contrast-associated adverse side effects

Both iodinated and gadolinium-based reagents can cause similar IV contrast-associated adverse side effects. The following categorizations can be applied to both types of contrast reagents. Nearly all contrast-associated side effects occur within 20 min of the injection of IV contrast [91]. The majority of these cases are mild non-life-threatening reactions. However, about 1 in 2500 patients will develop a severe and potentially life-threatening reaction to injected contrast [92]. Medical provider familiarity with acute reactions can help to identify and effectively manage these conditions when they occur. Contrast-associated adverse side effects can be categorized into allergic-like (anaphylactoid) or physiologic reactions. Allergic-like reactions are similar to allergic reactions (type I hypersensitivity) in their presentation, but some immunologic factors that are characteristic of a true allergic reaction are absent. Physiologic reactions are believed to be due to direct molecular toxicity and binding characteristics of the contrast media. Allergic-like reactions are further categorized by severity as mild, moderate, or severe (Table 6). Mild reactions are generally self-limiting and do not require medical intervention. Mild reactions include limited focal pruritis, limited urticaria, conjunctivitis, and rhinorrhea. Moderate reactions are more clinically prominent in presentation and often require medical intervention. Examples of moderate allergic-like reactions include diffuse pruritis, urticaria, bronchospasm, throat tightness, and facial edema. These reactions occur in the setting of normal vital signs. Severe reactions may cause significant morbidity and potential mortality. These reactions often require immediate medical intervention. Examples of severe reactions include pulmonary edema, anaphylactic shock, and hypotension. Pulmonary edema is a rare adverse reaction that can lead to severe cardiopulmonary collapse [93]. Anaphylactic shock has also been associated with IV contrast

administration. Patients who have previously received intravenous contrast without any adverse reactions can still subsequently develop anaphylaxis. In a study of 104 cases of contrast-induced anaphylaxis, 65.4% of patients who developed anaphylaxis had a history of uneventful previous exposure, whereas 34.6% of those patients developed anaphylaxis on their first exposure to contrast [94]. The American College of Radiology Manual on Contrast Media contains recommended interventions based on the type and severity of reactions [38].

## Premedication and allergies

The strongest predictor for development of an allergic-type reaction is a history of previous allergic-type reactions to IV contrast administration. In a retrospective study of 1178 patients who had a mild immediate hypersensitivity reaction to iodinated contrast, it was found that re-exposure to the same contrast agent was associated with a 31.1% recurrence rate in the absence of premedication [95]. Premedication is effective for reducing contrast reactions. In a multicenter randomized control trial, 6763 patients who received high-osmolar iodinated contrast were randomized to receive either one or two steroid pretreatment regimens vs the same number of placebo pills. Pretreatment using two doses of methylprednisolone significantly reduced the number of aggregate contrast reactions when compared to placebo (6.4% vs 9.9% on placebo  $p < 0.0001$ ) [96]. The authors repeated a second randomized control trial with newer low-osmolar contrast agents with a cohort of 1155 patients. They found that premedication significantly reduced mild and aggregate reactions [97]. However, this particular study was limited by inadequate power to evaluate reductions in moderate or severe reactions.

Patients with a history of allergies to seafood, “iodine,” or other medications do not require special precautions prior to administration of intravenous contrast. A common misconception is the need to premedicate patients with a history of seafood allergy, asthma, or “iodine allergy.” Seafood allergies are caused by IgE-mediated reactions to fish proteins such as tropomyosin whereas contrast allergies are due to activation of mast cells or basophils [98]. Because seafood allergies are mediated by a different physiological pathway, premedication is not indicated. Moreover, empiric studies have shown that patients with a seafood allergy do not have a significantly greater risk of developing an allergic-type contrast reaction compared to patients with other types of allergies [99, 100]. Similarly, a history of asthma does not require premedication. Bettmann et al. looked at 75,616 radiologic studies where patients received either low-osmolar contrast and high-osmolar contrast. Patients with well-controlled asthma were not at a significantly greater risk of developing a contrast reaction (OR 1.10,  $p > 0.05$ ) [101]. The concept of an “iodine allergy” continues

**Table 6** Categorization of contrast-associated adverse side effects. Adapted from the American College of Radiology (ACR) Manual on Contrast Media [38]

|                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                            |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mild ACRs: Signs and symptoms of a mild reaction are often self-limiting. These usually do not require medical intervention.                                                             |                                                                                                                                                                                                                                                                                                                                                            |
| Allergic                                                                                                                                                                                 | <ul style="list-style-type: none"> <li>• Sneezing, rhinorrhea, sinus congestion</li> <li>• Conjunctivitis</li> <li>• Limited throat irritation</li> <li>• Limited pruritis and urticaria</li> <li>• Transient soft tissue edema</li> </ul>                                                                                                                 |
| Physiologic                                                                                                                                                                              | <ul style="list-style-type: none"> <li>• Nausea, vomiting</li> <li>• Headache, anxiety, dizziness</li> <li>• Altered taste</li> <li>• Hypertension</li> <li>• Self-resolving vasovagal reaction</li> </ul>                                                                                                                                                 |
| Moderate ACRs: Signs and symptoms of moderate reactions are similar to those of mild reactions except that they often demonstrate progressive worsening while vital signs remain stable. |                                                                                                                                                                                                                                                                                                                                                            |
| Allergic                                                                                                                                                                                 | <ul style="list-style-type: none"> <li>• Diffuse pruritis and urticaria</li> <li>• Bronchospasm (no or mild hypoxia)</li> <li>• Diffuse cutaneous erythema</li> <li>• Throat tightness without dyspnea</li> </ul>                                                                                                                                          |
| Physiologic                                                                                                                                                                              | <ul style="list-style-type: none"> <li>• Prolonged nausea and vomiting</li> <li>• Chest pain</li> <li>• Hypertensive urgency</li> <li>• Vasovagal reaction responsive to medical intervention</li> </ul>                                                                                                                                                   |
| Severe ACRs: Severe reactions may be potentially life threatening, requiring timely recognition and medical intervention.                                                                |                                                                                                                                                                                                                                                                                                                                                            |
| Allergic                                                                                                                                                                                 | <ul style="list-style-type: none"> <li>• Diffuse soft tissue edema</li> <li>• Significant laryngeal edema causing hypoxia</li> <li>• Significant facial edema causing dyspnea or respiratory compromise</li> <li>• Bronchospasm with severe hypoxia</li> <li>• Anaphylaxis</li> <li>• Pulmonary edema that can lead to cardiopulmonary collapse</li> </ul> |
| Physiologic                                                                                                                                                                              | <ul style="list-style-type: none"> <li>• Hypertensive urgency</li> <li>• Seizures</li> <li>• Arrhythmia</li> <li>• Vasovagal reaction not responsive to treatment</li> </ul>                                                                                                                                                                               |

to be perpetuated in the medical field. Iodine is a naturally occurring ion that in many parts of the world has been incorporated into cooking salts. It is found in the human body, most commonly in thyroid hormones. It is not considered to be an allergen nor require premedication.

Because of the allergic-like nature of these reactions, immunologic skin testing has been proposed to screen patients for contrast reactions. Past studies of using skin testing to predict allergic-like contrast reactions have not been reliably predictable. In one study, 220 patients with a previous hypersensitivity reaction to contrast underwent intradermal skin testing where iodinated contrast was injected intradermally. The skin tests were found to have 96–100% specificity for acute reactions, but positive skin tests were only observed in 26% of patients who had acute reactions [102]. Because of its low sensitivity, immunologic skin testing cannot be used as a reliable screening tool.

Premedication in patients with a prior mild reaction is not required. Patients with a prior mild reaction will rarely have a more severe subsequent reaction. In a study of 133 patients with only isolated urticaria, subsequent re-exposure to the same contrast produced no severe reactions and no adverse reaction other than limited urticaria [103]. Patients with a previous mild allergic reaction have < 1% chance of developing a moderate or severe reaction [95]. Given the low risk of developing a more severe subsequent reaction, providers may opt to not premedicate for a previous mild reaction. In patients with a history of a moderate or severe contrast reaction, premedication with corticosteroids and antihistamine regimen should be strongly considered. Second-generation antihistamines such as cetirizine or fexofenadine are preferred over first-generation antihistamines such as diphenhydramine because of reduced sedative effects [104]. Sedative qualities of

first-generation antihistamines have been shown to cause significant impairment, especially in the setting of operating motor vehicles [105]. Second-generation antihistamines may be advantageous in reducing unnecessary observation time in the post-premedication setting. At present, there are no studies that directly compare the efficacy of diphenhydramine with a second-generation antihistamine in the setting of preventing acute contrast reactions. However, second-generation antihistamines have been repeatedly shown to be effective for reducing symptoms in patients with allergic rhinitis and urticaria [106–108]. Although premedication is effective for preventing contrast reactions, it is not a panacea. Patients can still experience breakthrough reactions, despite premedication. In a retrospective study, 1051 patients who completed a 13-h glucocorticoid and antihistamine premedication regimen prior to receiving low-osmolar iodinated contrast were examined for the rates of breakthrough reactions relative to the overall allergic-like reaction rate of the general population. Of the patients receiving premedication, 60% (626/1051) had a known previous reaction. The overall breakthrough reaction rate was found to be 1.2% (13/1051) with an estimated number needed to treat of 60 (95% CI 39–304) to prevent any one reaction [109].

Adults can be premedicated using an oral regimen consisting of methylprednisolone and cetirizine or fexofenadine (Algorithm 1). For pediatric patients, a weight-based approach is recommended for selecting a premedication regimen (Algorithm 2). In the emergency room setting, premedication has several limitations. One limitation of the standard oral premedication protocols is that they take at least 12 h to complete which may not be possible in an emergent setting. An accelerated premedication protocol using IV corticosteroid and IV diphenhydramine can be completed within 5 h prior to imaging (Algorithms 1 and 2). A retrospective cohort study comparing the 5-h IV steroid protocol to a 13-h oral regimen found that the IV steroids had similar rates of breakthrough reactions (2.5%, 95% CI 0.8–5.7%, vs 2.1%, 95% CI 1.1–3.5%) and were non-inferior to the oral regimen. Overall, all patients with a previous history of moderate or severe reactions should be considered for premedication. Patients with a history of only previous mild allergic-like reactions typically do not require premedication.

Patients who are pregnant with a history of moderate or severe contrast-associated adverse reactions may require premedication. Current practice guidelines do not differentiate between pregnant and non-pregnant patients—premedication recommendations are the same for both populations [38]. Similar to non-pregnant populations, antihistamines and steroids are the medications of choice for premedication. Antihistamines do not cross the placenta and have not been associated with birth defects [110]. In animal studies, prednisone is associated with adverse effects on the fetus although there are currently no adequate studies evaluating its effects in

humans [38]. Current expert opinion considers steroids to be a safe regimen for premedication when the benefits of IV contrast administration and premedication outweigh the risks and alternate imaging cannot answer the clinical question [111].

## Summary

In the emergency department setting, the use of IV contrast should be based on patient needs and should not be denied without assessment of the patient's risk factors and consideration of new guidelines for use of IV contrast agents. The greatest risk factors for adverse side effects to contrast use are poor renal function and previous moderate or severe allergic-type reaction to IV contrast injection. The use of effective screening tools can help emergency room providers quickly determine the need for further laboratory evaluation prior to imaging. Premedication can significantly help to reduce adverse reactions especially in patients with a known history of prior moderate or severe contrast reaction. Acute contrast reactions are relatively rare. But familiarity with the types of contrast-associated adverse reactions can lead to faster recognition and timely appropriate management.

**Algorithm 1.** Premedication decision-making tool for adults using severity of previous allergic-type reaction

**Algorithm 2.** Premedication decision-making tool for pediatric patients

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

## References

1. Richmond C (2004) Sir Godfrey Hounsfield. *BMJ* 329:687. <https://doi.org/10.1136/bmj.329.7467.687>
2. United States Health Resources Administration, National Center for Health Statistics (U.S.) (1992) Advance data. -Apr 23, 1980, DHEW Publ no
3. OECD (2017) Health at a glance 2015: OECD indicators. OECD Publ. [https://doi.org/health\\_glance-2015-en](https://doi.org/health_glance-2015-en)
4. Pasternak JJ, Williamson EE (2012) Clinical pharmacology, uses, and adverse reactions of iodinated contrast agents: a primer for the non-radiologist. *Mayo Clin Proc*
5. Wang CL, Cohan RH, Ellis JH et al (2008) Frequency, outcome, and appropriateness of treatment of nonionic iodinated contrast media reactions. *Am J Roentgenol*. <https://doi.org/10.2214/AJR.07.3421>
6. Katayama H, Yamaguchi K, Kozuka T et al (1990) Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. *Radiology*. <https://doi.org/10.1148/radiology.175.3.2343107>

7. Jung J-W, Kang H-R, Kim M-H et al (2012) Immediate hypersensitivity reaction to gadolinium-based MR contrast media. *Radiology*. <https://doi.org/10.1148/radiol.12112025>
8. National Center for Health Statistics (2017) Health United States report 2016
9. Tepel M, Aspelin P, Lameire N (2006) Contrast-induced nephropathy: a clinical and evidence-based approach. *Circulation*. <https://doi.org/10.1161/CIRCULATIONAHA.105.595090>
10. Bartels ED, Brun GC, Gammeltoft A, Gjørup PA (1954) Acute anuria following intravenous pyelography in a patient with myelomatosis. *Acta Med Scand*. <https://doi.org/10.1111/j.0954-6820.1954.tb18632.x>
11. Killmann S-A, Gjørup S, Thaysen JH (1957) Fatal acute renal failure following intravenous pyelography in a patient with multiple myeloma. *Acta Med Scand*. <https://doi.org/10.1111/j.0954-6820.1957.tb15742.x>
12. Khwaja A (2012) KDIGO clinical practice guidelines for acute kidney injury. *Nephron - Clin. Pract*
13. Bruce RJ, Djamali A, Shinki K et al (2009) Background fluctuation of kidney function versus contrast-induced nephrotoxicity. *Am J Roentgenol*. <https://doi.org/10.2214/AJR.08.1413>
14. Heller CA, Knapp J, Halliday J et al (1991) Failure to demonstrate contrast nephrotoxicity. *Med J Aust*
15. Langner S, Stumpe S, Kirsch M et al (2008) No increased risk for contrast-induced nephropathy after multiple CT perfusion studies of the brain with a nonionic, dimeric, iso-osmolal contrast medium. *Am J Neuroradiol*. <https://doi.org/10.3174/ajnr.A1164>
16. Lima FO, Lev MH, Levy RA et al (2010) Functional contrast-enhanced CT for evaluation of acute ischemic stroke does not increase the risk of contrast-induced nephropathy. *Am J Neuroradiol*. <https://doi.org/10.3174/ajnr.A1927>
17. McGillicuddy EA, Schuster KM, Kaplan LJ et al (2010) Contrast-induced nephropathy in elderly trauma patients. *J Trauma - Inj Infect Crit Care*. <https://doi.org/10.1097/TA.0b013e3181cf7e40>
18. Oleinik A, Romero JM, Schwab K et al (2009) CT angiography for intracerebral hemorrhage does not increase risk of acute nephropathy. *Stroke*. <https://doi.org/10.1161/STROKEAHA.108.546127>
19. Tremblay LN, Tien H, Hamilton P et al (2005) Risk and benefit of intravenous contrast in trauma patients with an elevated serum creatinine. *J Trauma - Inj Infect Crit Care*. <https://doi.org/10.1097/01.ta.0000194694.71607.0c>
20. Newhouse JH, Kho D, Rao QA, Starren J (2008) Frequency of serum creatinine changes in the absence of iodinated contrast material: implications for studies of contrast nephrotoxicity. *Am J Roentgenol*. <https://doi.org/10.2214/AJR.07.3280>
21. Katzberg RW, Newhouse JH (2010) Intravenous contrast medium-induced nephrotoxicity: is the medical risk really as great as we have come to believe? *Radiology*. <https://doi.org/10.1148/radiol.10092000>
22. Katzberg RW, Lamba R (2009) Contrast-induced nephropathy after intravenous administration: fact or fiction? *Radiol Clin N Am* 47:789–800. <https://doi.org/10.1016/j.rcl.2009.06.002>
23. Davenport MS, Khalatbari S, Cohan RH et al (2013) Contrast material-induced nephrotoxicity and intravenous low-osmolality iodinated contrast material: risk stratification by using estimated glomerular filtration rate. *Radiology*. <https://doi.org/10.1148/radiol.13122276>
24. Davenport MS, Khalatbari S, Dillman JR et al (2013) Contrast material-induced nephrotoxicity and intravenous low-osmolality iodinated contrast material. *Radiology*. <https://doi.org/10.1148/radiol.12121394>
25. McDonald JS, McDonald RJ, Carter RE et al (2014) Risk of intravenous contrast material-mediated acute kidney injury: a propensity score-matched study stratified by baseline-estimated glomerular filtration rate. *Radiology*. <https://doi.org/10.1148/radiol.13130775>
26. McDonald RJ, McDonald JS, Bida JP, Carter RE, Fleming CJ, Misra S, Williamson EE, Kallmes DF (2013) Intravenous contrast material-induced nephropathy: causal or coincident phenomenon? *Radiology* 267:106–118. <https://doi.org/10.1148/radiol.12121823>
27. Hinson JS, Ehmann MR, Fine DM et al (2017) Risk of acute kidney injury after intravenous contrast media administration. *Ann Emerg Med*. <https://doi.org/10.1016/j.annemergmed.2016.11.021>
28. ACR Committee on Drugs and Contrast Media (2018) ACR manual on contrast media version 10.3
29. Evola S, Lunetta M, MacAione F et al (2012) Risk factors for contrast induced nephropathy: a study among italian patients. *Indian Heart J*. <https://doi.org/10.1016/j.ihj.2012.07.007>
30. Mueller C, Buerkle G, Buettner HJ et al (2002) Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. *Arch Intern Med*
31. Trivedi HS, Moore H, Nasr S et al (2004) A randomized prospective trial to assess the role of saline hydration on the development of contrast nephrotoxicity. *Nephron Clin Pract*. <https://doi.org/10.1159/000066641>
32. Weisbord SD, Palevsky PM (2008) Prevention of contrast-induced nephropathy with volume expansion. *Clin J Am Soc Nephrol*
33. Solomon RJ, Natarajan MK, Doucet S et al (2007) Cardiac Angiography in Renally Impaired Patients (CARE) study: a randomized double-blind trial of contrast-induced nephropathy in patients with chronic kidney disease. *Circulation*. <https://doi.org/10.1161/CIRCULATIONAHA.106.671644>
34. Merten GJ, Burgess WP, Gray LV et al (2004) Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *J Am Med Assoc*. <https://doi.org/10.1001/jama.291.19.2328>
35. Ozcan EE, Guneri S, Akdeniz B et al (2007) Sodium bicarbonate, N-acetylcysteine, and saline for prevention of radiocontrast-induced nephropathy. A comparison of 3 regimens for protecting contrast-induced nephropathy in patients undergoing coronary procedures. A single-center prospective controlled. *Am Heart J*. <https://doi.org/10.1016/j.ahj.2007.05.012>
36. From AM, Bartholmai BJ, Williams AW et al (2008) Sodium bicarbonate is associated with an increased incidence of contrast nephropathy: a retrospective cohort study of 7977 patients at Mayo Clinic. *Clin J Am Soc Nephrol*. <https://doi.org/10.2215/CJN.03100707>
37. Maioli M, Toso A, Leoncini M et al (2008) Sodium bicarbonate versus saline for the prevention of contrast-induced nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. *J Am Coll Cardiol*. <https://doi.org/10.1016/j.jacc.2008.05.026>
38. American College of Radiology (2017) ACR manual on contrast media
39. Kolli P, Elicker B, Coakley F, et al (2018) UCSF CT and X-ray contrast guidelines
40. Tippins RB, Torres WE, Baumgartner BR, Baumgarten DA (2013) Are screening serum creatinine levels necessary prior to outpatient CT examinations? *Radiology*. <https://doi.org/10.1148/radiology.216.2.r00au23481>
41. Andreucci M, Faga T, Pisani A et al (2014) Prevention of contrast-induced nephropathy through a knowledge of its pathogenesis and risk factors. *Sci World J*
42. Rear R, Bell RM, Hausenloy DJ (2016) Contrast-induced nephropathy following angiography and cardiac interventions. *Heart*. <https://doi.org/10.1136/heartjnl-2014-306962>

43. Deray G (2006) Dialysis and iodinated contrast media. *Kidney Int.* <https://doi.org/10.1038/sj.ki.5000371>
44. Younathan CM, Kaude JV, Cook MD et al (1994) Dialysis is not indicated immediately after administration of nonionic contrast agents in patients with end-stage renal disease treated by maintenance dialysis. *Am J Roentgenol.* <https://doi.org/10.2214/ajr.163.4.8092045>
45. Hamani A, Petitclerc T, Jacobs C, Deray G (1998) Is dialysis indicated immediately after administration of iodinated contrast agents in patients on haemodialysis? *Nephrol Dial Transplant*
46. Vogt B, Ferrari P, Schönholzer C et al (2001) Prophylactic hemodialysis after radiocontrast media in patients with renal insufficiency is potentially harmful. *Am J Med.* [https://doi.org/10.1016/S0002-9343\(01\)00983-4](https://doi.org/10.1016/S0002-9343(01)00983-4)
47. Cruz DN, Goh CY, Marenzi G et al (2012) Renal replacement therapies for prevention of radiocontrast-induced nephropathy: a systematic review. *Am J Med*
48. Baerlocher MO, Asch M, Myers A (2013) Metformin and intravenous contrast. *CMAJ.* <https://doi.org/10.1503/cmaj.090550>
49. Goergen SK, Rumbold G, Compton G, Harris C (2009) Systematic review of current guidelines, and their evidence base, on risk of lactic acidosis after administration of contrast medium for patients receiving metformin. *Radiology.* <https://doi.org/10.1148/radiol.09090690>
50. Misbin RI (2004) The phantom of lactic acidosis due to metformin in patients with diabetes. *Diabetes Care*
51. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE (2010) Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev*
52. Turner R (1998) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet.* [https://doi.org/10.1016/S0140-6736\(98\)07037-8](https://doi.org/10.1016/S0140-6736(98)07037-8)
53. Knowler WC, Barrett-Connor E, Fowler SE et al (2002) Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* <https://doi.org/10.1056/NEJMoa012512>
54. Eppenga WL, Lalmohamed A, Geerts AF et al (2014) Risk of lactic acidosis or elevated lactate concentrations in metformin users with renal impairment: a population-based cohort study. *Diabetes Care.* <https://doi.org/10.2337/dc13-3023>
55. Lazarus B, Wu A, Shin JI et al (2018) Association of metformin use with risk of lactic acidosis across the range of kidney function: a community-based cohort study. *JAMA Intern Med.* <https://doi.org/10.1001/jamainternmed.2018.0292>
56. Bell S, Farran B, McGurnaghan S, McCrimmon RJ, Leese GP, Petrie JR, McKeigue P, Sattar N, Wild S, McKnight J, Lindsay R, Colhoun HM, Looker H (2017) Risk of acute kidney injury and survival in patients treated with metformin: an observational cohort study. *BMC Nephrol* 18:1–8. <https://doi.org/10.1186/s12882-017-0579-5>
57. Angioi A, Cabiddu G, Conti M, Pili G, Atzeni A, Matta V, Cao R, Floris M, Songini M, Mulas MF, Rosner M, Pani A (2018) Metformin associated lactic acidosis: a case series of 28 patients treated with sustained low-efficiency dialysis (SLED) and long-term follow-up. *BMC Nephrol* 19:1–7. <https://doi.org/10.1186/s12882-018-0875-8>
58. Runge VM, Stewart RG, Clanton JA et al (1983) Work in progress: potential oral and intravenous paramagnetic NMR contrast agents. *Radiology.* <https://doi.org/10.1148/radiology.147.3.6844614>
59. Brasch RC, Nitecki DE, Brant Zawadzki M (1983) Brain nuclear magnetic resonance imaging enhanced by a paramagnetic nitroxide contrast agent: preliminary report. *Am J Neuroradiol*
60. Lohrke J, Frenzel T, Endrikat J et al (2016) 25 years of contrast-enhanced MRI: developments, current challenges and future perspectives. *Adv Ther*
61. Murphy KJ, Brunberg JA, Cohan RH (1996) Adverse reactions to gadolinium contrast media: a review of 36 cases. *Am J Roentgenol.* <https://doi.org/10.2214/ajr.167.4.8819369>
62. Quinn AD, O'Hare NJ, Wallis FJ, Wilson GF (1994) Gd-dtpa: an alternative contrast medium for ct. *J Comput Assist Tomogr.* <https://doi.org/10.1097/00004728-199407000-00022>
63. Cowper SE, Robin HS, Steinberg SM et al (2000) Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. *Lancet.* [https://doi.org/10.1016/S0140-6736\(00\)02694-5](https://doi.org/10.1016/S0140-6736(00)02694-5)
64. Kucher C, Steere J, Elenitsas R, Siegel DL, Xu X (2006) Nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis with diaphragmatic involvement in a patient with respiratory failure. *J Am Acad Dermatol* 54:S31–S34. <https://doi.org/10.1016/j.jaad.2005.04.024>
65. Ting WW, Stone MS, Madison KC, Kurtz K (2003) Nephrogenic fibrosing dermopathy with systemic involvement. *Arch Dermatol* 139:903–906. <https://doi.org/10.1001/archderm.139.7.903>
66. Grobner T (2006) Gadolinium – a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant.* <https://doi.org/10.1093/ndt/gfk062>
67. Marckmann P, Skov L, Rossen K et al (2006) Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. *J Am Soc Nephrol.* <https://doi.org/10.1681/asn.2006060601>
68. Kanda T, Ishii K, Kawaguchi H et al (2014) High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. *Radiology.* <https://doi.org/10.1148/radiol.13131669>
69. Wertman R, Altun E, Martin DR et al (2008) Risk of nephrogenic systemic fibrosis: evaluation of gadolinium chelate contrast agents at four American universities. *Radiology.* <https://doi.org/10.1148/radiol.2483072093>
70. Robert P, Violas X, Grand S et al (2016) Linear gadolinium-based contrast agents are associated with brain gadolinium retention in healthy rats. *Investig Radiol.* <https://doi.org/10.1097/RLI.0000000000000241>
71. Endrikat J, Dohanish S, Schleyer N et al (2018) 10 years of nephrogenic systemic fibrosis. *Investig Radiol.* <https://doi.org/10.1097/rli.0000000000000462>
72. Broome DR, Girguis MS, Baron PW et al (2007) Gadodiamide-associated nephrogenic systemic fibrosis: why radiologists should be concerned. *Am J Roentgenol*
73. Sadowski EA, Bennett LK, Chan MR et al (2007) Nephrogenic systemic fibrosis: risk factors and incidence estimation. *Radiology.* <https://doi.org/10.1148/radiol.2431062144>
74. Wang Y, Alkasab TK, Narin O, et al (2011) Incidence of nephrogenic systemic fibrosis after adoption of restrictive gadolinium-based contrast agent guidelines. *Int. Braz J Urol*
75. Tombach B, Bremer C, Reimer P et al (2002) Using highly concentrated gadobutrol as an MR contrast agent in patients also requiring hemodialysis: safety and dialysability. *Am J Roentgenol.* <https://doi.org/10.2214/ajr.178.1.1780105>
76. Reilly RF (2008) Risk for nephrogenic systemic fibrosis with gadoteridol (ProHance) in patients who are on long-term hemodialysis. *Clin J Am Soc Nephrol.* <https://doi.org/10.2215/CJN.05721207>
77. Martin DR, Krishnamoorthy SK, Kalb B et al (2010) Decreased incidence of NSF in patients on dialysis after changing gadolinium contrast-enhanced MRI protocols. *J Magn Reson Imaging.* <https://doi.org/10.1002/jmri.22024>

78. McDonald RJ, McDonald JS, Kallmes DF et al (2015) Gadolinium deposition in human brain tissues after contrast-enhanced MR imaging in adult patients without intracranial abnormalities. *Radiology*. <https://doi.org/10.1148/radiol.2017161595>
79. Layne KA, Dargan PI, Archer JRH, Wood DM (2018) Gadolinium deposition and the potential for toxicological sequelae – a literature review of issues surrounding gadolinium-based contrast agents. *Br J Clin Pharmacol*
80. Ersoy H, Rybicki FJ (2007) Biochemical safety profiles of gadolinium-based extracellular contrast agents and nephrogenic systemic fibrosis. *J Magn Reson Imaging*
81. Kubik-Huch RA, Gottstein-Aalame NM, Frenzel T et al (2000) Gadopentetate dimeglumine excretion into human breast milk during lactation. *Radiology*. <https://doi.org/10.1148/radiology.216.2.r00au09555>
82. Nielsen ST, Matheson I, Rasmussen JN et al (1987) Excretion of iohexol and metrizoate in human breast milk. *Acta Radiol*. <https://doi.org/10.3109/02841858709177394>
83. Webb JAW, Thomsen HS, Morcos SK et al (2005) The use of iodinated and gadolinium contrast media during pregnancy and lactation. *Eur Radiol*. <https://doi.org/10.1007/s00330-004-2583-y>
84. Rofsky NM, Weinreb JC, Litt AW (1993) Quantitative analysis of gadopentetate dimeglumine excreted in breast milk. *J Magn Reson Imaging*. <https://doi.org/10.1002/jmri.1880030122>
85. SHAW DD, POTTS DG (1985) Toxicology of iohexol. *Investig Radiol*. <https://doi.org/10.1097/00004424-198501002-00004>
86. Ralston WH, Robbins MS, James P (1989) Reproductive, developmental, and genetic toxicology of ioversol. *Investig Radiol*
87. Rajaram S, Exley CE, Fairlie F, Matthews S (2012) Effect of antenatal iodinated contrast agent on neonatal thyroid function. *Br J Radiol*. <https://doi.org/10.1259/bjr/29806327>
88. Bourjeily G, Chalhoub M, Phomphutkul C et al (2010) Neonatal thyroid function: effect of a single exposure to iodinated contrast medium in utero. *Radiology*. <https://doi.org/10.1148/radiol.10100163>
89. Rofsky NM, Pizzarello DJ, Weinreb JC et al (1994) Effect on fetal mouse development of exposure to MR imaging and gadopentetate dimeglumine. *J Magn Reson Imaging*. <https://doi.org/10.1002/jmri.1880040611>
90. Ray JG, Vermeulen MJ, Bharatha A et al (2016) Association between MRI exposure during pregnancy and fetal and childhood outcomes. *JAMA - J Am Med Assoc*. <https://doi.org/10.1001/jama.2016.12126>
91. Thomsen HS (2016) How to manage (treat) immediate-type adverse reactions to GBCA. *Top Magn Reson Imaging*
92. William HB, Sega AJ (2009) Recognition and treatment of acute contrast reactions. *Appl Radiol*
93. Guru PK, Bohman JK, Fleming CJ et al (2016) Severe acute cardiopulmonary failure related to gadobutrol magnetic resonance imaging contrast reaction: successful resuscitation with extracorporeal membrane oxygenation. *Mayo Clin Proc*. <https://doi.org/10.1016/j.mayocp.2015.12.010>
94. Kim MH, Lee SY, Lee SE et al (2014) Anaphylaxis to iodinated contrast media: clinical characteristics related with development of anaphylactic shock. *PLoS One*. <https://doi.org/10.1371/journal.pone.0100154>
95. Park S-J, Kang D-Y, Sohn K-H et al (2018) Immediate mild reactions to CT with iodinated contrast media: strategy of contrast media readministration without corticosteroids. *Radiology*. <https://doi.org/10.1148/radiol.2018172524>
96. Lasser EC, Berry CC, Talner LB, Santini LC, Lang EK, Gerber FH, Stolberg HO (1987) Pretreatment with corticosteroids to alleviate reactions to intravenous contrast material. *N Engl J Med* 317: 845–849. <https://doi.org/10.1056/NEJM198710013171401>
97. Lasser EC, Berry CC, Mishkin MM, et al (1994) Pretreatment with corticosteroids to prevent adverse reactions to nonionic contrast media. *Am J Roentgenol*
98. Lee AJ, Gerez I, Shek LPC, Lee BW (2012) Shellfish allergy - an Asia-Pacific perspective. *Asian Pacific J. Allergy Immunol*
99. Shehadi WH (1974) Adverse reactions to Intravascularly administered contrast media: a comprehensive study based on a prospective survey. *Am Roentgen Ray Soc*
100. Beaty AD, Lieberman PL, Slavin RG (2008) Seafood allergy and radiocontrast media: are physicians propagating a myth? *Am J Med*. <https://doi.org/10.1016/j.amjmed.2007.08.025>
101. Bettmann MA, Heeren T, Greenfield A, Goudey C (1994) Adverse events with radiographic contrast agents: results of the SCVIR contrast agent registry. *Radiology*. <https://doi.org/10.1148/radiology.203.3.9169677>
102. Brockow K, Christiansen C, Kanny G, et al (2005) Management of hypersensitivity reactions to iodinated contrast media. *Allergy Eur J Allergy Clin Immunol*
103. Kolbe AB, Hartman RP, Hoskin TL, Carter RE, Maddox DE, Hunt CH, Hesley GK (2014) Premedication of patients for prior urticarial reaction to iodinated contrast medium. *Abdom Imaging* 39:432–437. <https://doi.org/10.1007/s00261-013-0058-9>
104. Church MK, Maurer M, Simons FER et al (2010) Risk of first-generation H1-antihistamines: a GA2LEN position paper. *Allergy* 65:459–466. <https://doi.org/10.1111/j.1398-9995.2009.02325.x>
105. Inami A, Matsuda R, Grobosch T et al (2016) A simulated car-driving study on the effects of acute administration of levocetirizine, fexofenadine, and diphenhydramine in healthy Japanese volunteers. *Hum Psychopharmacol*. <https://doi.org/10.1002/hup.2524>
106. Park JH, Godbold JH, Chung D et al (2011) Comparison of cetirizine and diphenhydramine in the treatment of acute food-induced allergic reactions. *J Allergy Clin Immunol*. <https://doi.org/10.1016/j.jaci.2011.08.026>
107. Simons FER, Simons KJ (2011) Histamine and H1-antihistamines: celebrating a century of progress. *J Allergy Clin Immunol*
108. Simons FER (2004) Advances in H 1 -antihistamines. *N Engl J Med*. <https://doi.org/10.1056/nejmra033121>
109. Mervak BM, Davenport MS, Ellis JH, Cohan RH (2015) Rates of breakthrough reactions in inpatients at high risk receiving premedication before contrast-enhanced CT. *Am J Roentgenol*. <https://doi.org/10.2214/AJR.14.13810>
110. Horowitz JM, Bisla JK, Yaghmai V (2016) Premedication of pregnant patients with history of iodinated contrast allergy. *Abdom Radiol* 41:2424–2428. <https://doi.org/10.1007/s00261-016-0843-3>
111. Gerosa M, Meroni PL, Cimaz R (2014) Safety considerations when prescribing immunosuppression medication to pregnant women. *Expert Opin Drug Saf*

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