



Practical administration of intravenous contrast media in children: screening, prophylaxis, administration and treatment of adverse reactions

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Received: 6 July 2018 / Revised: 14 September 2018 / Accepted: 2 November 2018 / Published online: 14 March 2019
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Abstract

Administration of intravenous contrast media to children is a routine practice at many clinical imaging centers, that can involve special considerations. In this paper, we provide practical information to facilitate optimal performance and oversight of this task. We provide targeted screening questions that can help to identify high-risk pediatric patients for both iodine-based and gadolinium-based intravenous contrast media administration. These include children at risk for allergic-like reactions, thyroid dysfunction, contrast-induced nephropathy, and nephrogenic systemic fibrosis. We make recommendations for addressing “yes” responses to screening questions using risk stratification schema that are specific to children. We also present criteria for selecting children for premedication prior to intravenous contrast administration, and suggest pediatric regimens. Additionally, we discuss practical nuances of intravenous contrast media administration to children and provide a quick-reference table of appropriate treatments with pediatric dosages for adverse contrast reactions.

Keywords Adverse reaction · Children · Contrast agent · Gadolinium-based contrast media · Intravenous · Iodine-based contrast media · Prophylaxis · Screening

Introduction

The *American College of Radiology (ACR) Manual on Contrast Media*, currently in its 10th edition, describes distinct considerations regarding intravenous contrast media use and management of associated adverse events in the pediatric

population [1]. A chapter dedicated to contrast media in children primarily focuses on the treatment and incidence of allergic-like reactions and contrast-induced nephropathy. There are, however, additional nuances to the administration of intravenous contrast media in the pediatric population that should be familiar to all practicing radiologists. In this manuscript, we review literature on the administration of intravenous iodine-based contrast media (IBCM) and gadolinium-based contrast media (GBCM) in children, and provide summative tools for quick reference during clinical workflow. Specifically, we address screening children prior to contrast media administration, prophylaxis and treatment of adverse reactions, and technical considerations in the administration of contrast media. Recent assessments of practice patterns at pediatric hospitals show predominant use of nonionic, low-osmolar IBCM [2], as well as macrocyclic GBCM [3], and when possible we limit our discussion to more recent data relevant to these media.

Screening questions

An individualized assessment of the risks and benefits of intravenous contrast media administration, with a consideration

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of possible alternatives, is an essential component of the pre-imaging workup for each pediatric patient. For most children, intravenous contrast media are well tolerated and require no special attention for appropriate indications. However, a standardized list of pre-imaging screening questions, posed to the child and family, can help to identify children who require additional consideration to optimize contrast media administration to his or her specific needs. An example list of screening questions for pediatric patient populations is presented in

Table 1 (see also Tables 2, 3, 4, and 5), based on relevant literature discussed next.

Allergic-like reactions

The incidence of moderate-to-severe allergic-like reactions to intravenous IBCM and GBCM in pediatric patients is very low, on the order of 0.04–0.10% [11, 12] and 0.02–0.03%

Table 1 Screening questions for families of pediatric patients prior to intravenous contrast administration and action items for positive screening results

IBCM or GBCM screening questions

1. Allergy to IV contrast media? If yes, what was the reaction? Did you receive any treatment for it?
 - If yes, ensure the appropriate precautions have been taken prior to administration of intravenous contrast media based on risk category^a. If an appropriate premedication regimen has not been administered, contact the referring clinician prior to contrast administration
2. Active asthma symptoms (wheezing, shortness of breath)?
 - If yes, the examination should be performed at a facility where a code team is immediately available unless the same class of intravenous contrast media has been previously administered without incident
3. Other moderate or severe allergies to food or medications?
 - If yes, the examination should be performed at a facility where a code team is immediately available, unless the same class of intravenous contrast media has been previously administered without incident
4. Kidney transplant, single kidney, kidney cancer, dialysis, diabetes mellitus, high blood pressure requiring medication, surgery within the last 6 weeks, other kidney problems^b?
 - Dialysis
 - If anuric, proceed
 - If oliguric, discuss with referring clinician prior to IBCM administration
 - If administering GBCM, coordinate a prompt dialysis session following the exam, as this may reduce the risk of nephrogenic systemic fibrosis
 - If yes to a different question, same action items as Question 5
5. Acute illness (e.g., multiple episodes of vomiting/diarrhea or unable to eat or drink for 24 hours or more within the last week)?
 - If yes, check recent^c serum creatinine and calculate eGFR^d (eGFR is not helpful in the context of acute kidney injury [AKI] or dialysis)
 - If AKI or CKD^e, discuss with referring clinician or nephrologist prior to contrast administration

Additional IBCM questions

6. IV contrast exposure in the last 48 hours?
 - If yes, there is a potentially increased risk of CIN when administering additional doses. If the patient has additional risk factors for CIN (see questions 4 and 5), discuss with referring clinician prior to repeat contrast administration, unless the study is emergent
7. Thyroid dysfunction?
 - Consider discussion of potential risk of superimposed iodine-induced thyroid dysfunction with referring clinician
8. Thyroid cancer or Graves disease?
 - Confirm that radioactive iodine nuclear medicine study or therapy is not planned for at least 2 months following IBCM administration
9. Metformin use?
 - If risk factors for, or laboratory evidence of, AKI or severe CKD^e, discuss with referring clinician prior to IBCM administration
 - Metformin should be stopped at the time of IBCM administration and held for at least 48 hours in patients with AKI or eGFR <30 mL/min per 1.73m². The drug should be reinstated only after adequate renal function has been confirmed

AKI acute kidney injury, CIN contrast induced nephropathy, CKD chronic kidney disease, cm centimeters, dL deciliters, eGFR estimated glomerular filtration rate, GBCM gadolinium-based contrast media, IBCM iodine-based contrast media, IV intravenous, mg milligrams

^a See Table 2

^b Check for other conditions that might result in CKD, such as renal hypoplasia/dysplasia, cystic kidney diseases, renal parenchymal scarring or chronic glomerulonephritides. Note that uncomplicated cystitis, benign familial hematuria, and simple cysts are not significant risk factors

^c See Table 3

^d Estimated glomerular filtration rate (eGFR) can be calculated online (e.g., https://www.kidney.org/professionals/kdoqi/gfr_calculatorped) or by hand with the modified Schwartz equation [5]: eGFR = (0.413*height in cm)/serum creatinine in mg/dL

^e See Table 4

Table 2 Risk stratification and prophylactic measures for allergic-like reactions to intravenous contrast media

Risk category	Criteria	Premedication and precautions
I (low risk)	• Prior severe allergic reaction to a single food or medication (e.g., shellfish, peanuts, penicillin), including anaphylaxis • Prior moderate to severe reaction to a different class of contrast media (e.g., allergic-like reaction to GBCM and receiving IBCM) • Family history of severe allergy to the same class of contrast media • History of asthma • Multiple moderate or severe allergies to food or medications, but prior exposure to the same class of contrast media was well tolerated	• Premedication and special precautions are typically unnecessary
II (low to moderate risk)	• Active asthma symptoms • Multiple moderate or severe allergies to food or medications and no prior exposure to the same class of contrast media	• Premedication is typically unnecessary • Consider performing the initial study at a location where a code team is immediately available (e.g., hospital setting). If well-tolerated, subsequent studies involving the same class of contrast media could be performed without this precaution
III (moderate risk)	• Prior mild reaction to the same class of contrast media, including limited cutaneous reaction (e.g., a few hives, mild edema), “itchy” or “scratchy” throat, nasal congestion, sneezing, conjunctivitis, etc. • Prior moderate reaction to the same class of contrast media, including upper airway edema, breathing difficulty, bronchospasm, diffuse cutaneous reaction (e.g., many hives), throat tightness or hoarseness, but stable vital signs	• Premedication and/or alternative imaging strategies are recommended^a • A radiology provider should consider providing the child/family with written information regarding the risk of breakthrough reactions despite pre-medication, and ensure they have received an appropriate pre-medication regimen^b • Consider performing the study at a location where a code team is available • Providers must be prepared to treat an allergic-like or anaphylactoid reaction
IV (high risk)	• Prior severe reaction to the same class of contrast media, including cardiovascular collapse, wheezing or bronchospasm with significant hypoxia, anaphylactic shock, diffuse edema or facial edema with dyspnea, diffuse erythema with hypotension	• Alternative imaging strategies and avoidance of the inciting contrast media are strongly recommended.^a If the specific contrast medium that elicited a severe reaction is known, a contrast medium from a different class should be considered if possible (e.g., IBCM instead of GBCM and vice versa) • If a given imaging study and associated contrast media are deemed to be emergent and there are no viable imaging or contrast alternatives, utilization of different contrast media within the same class is strongly recommended^a • If the same class of contrast media needs to be used, premedication is strongly recommended^a if possible, but providers still must be prepared to treat a serious anaphylactoid reaction • Consider obtaining written informed consent from the child/family, including information regarding the risks of breakthrough reaction despite pre-medication. Completion of an appropriate pre-medication regimen should be verified^{a,b} • The study should be performed at a location where a code team is available

GBCM gadolinium-based contrast media, IBCM iodine-based contrast media

^a Alternative imaging strategies involving different class (e.g., gadolinium-enhanced MRI or contrast-enhanced ultrasound if the child has a history of reaction to iodine-based contrast media) or a non-contrast protocol should always be considered for children with moderate- or high-level risk stratification. In the rare clinical scenario where the benefit of acquiring an immediate contrast-enhanced exam involving a contrast medium that has previously evoked a severe reaction outweighs the risk of recurrent reaction without premedication (e.g., child with a history of reaction to IBCM, and clinical concern for severe injury in the context of a motor vehicle accident or stroke), premedication and informed consent procedures can be forgone provided a code team is available during the injection to monitor for and appropriately manage a reaction

^b See Table 5 for appropriate pediatric premedication regimens

Table 3 Proposed timing of serum creatinine measurement prior to intravenous contrast administration

Patient type	+Kidney risk factors ^a	No risk factors
Outpatients and emergency patients	+Acute illness ^a :	24 hours
	No acute illness:	14 days
Inpatients	Within 24 hours	Not required

^a See Table 1, questions 4 and 5 for example risk factors and definition of “acute illness” that would place the child at risk for acute kidney injury

[13–15], respectively. The ACR recommends screening for the same factors in both adults and children that might increase risk of these reactions [1].

Immediate reactions occurring less than 1 hour after administration were initially thought to be anaphylactoid rather than a true immunoglobulin E (Ig-E)-mediated reactions; however more recent literature provides evidence of histamine and tryptase release as well as positive skin tests to radiocontrast agents, suggesting a potential mechanism for Ig-E-mediated allergy, even for immediate reactions [16]. Reactions likely occur through both Ig-E-mediated and non-Ig-E-mediated histamine release. Notably, no prior exposure is required for an

allergic-like reaction to intravenous contrast media, and reactions are thought to be independent of dose, concentration and rate of infusion.

The vast majority of allergic-like reactions are dermatological, including urticaria and pruritus. Anaphylactoid reactions are clinically indistinguishable from true anaphylaxis. Minor anaphylactoid reactions include nausea and vomiting, urticaria and pruritus. Moderate reactions also include facial edema, laryngeal edema and bronchospasm. Severe anaphylactoid reactions are characterized by hypotensive shock, pulmonary edema, respiratory or cardiac arrest and seizures [17–20]. Serious potentially life-

Table 4 Assessment of renal function in children with positive screening results

Chronic kidney disease (CKD)

Below these age-based eGFR thresholds (mL/min per 1.73 m²), discuss with referring clinician or nephrologist prior to intravenous contrast administration^a:

- <2 years of age: eGFR more than 2 standard deviations below age-based normal ranges [6]
- 2–18 years of age: 75

By the 2012 KDIGO guidelines [7], CKD is defined as abnormalities of kidney structure or function, present for >3 months. This might include children with one of the following criteria:

- There is evidence of structural damage on imaging or pathological abnormalities on histology
- There are other kidney function abnormalities (albuminuria, renal tubular disorders)
- The child has a functional kidney transplant
- GFR <60 mL/min per 1.73 m²

Acute kidney injury (AKI)

The 2012 KDIGO guidelines [8] and the ACR [1] use the following criteria to define AKI in children:

- Absolute serum creatinine increase ≥ 0.3 mg/dL (>26.5 micromol/L) within 48 hours, or
- Increase in serum creatinine ≥ 1.5 -fold above baseline, which is known or presumed to have occurred within the prior 7 days, or
- Urine output reduced to ≤ 0.5 mL/kg/h for 6 hours

The lowest serum creatinine value obtained in the last 3 months should be used as the baseline [9]. When no prior serum creatinine values are available, use the upper limit of age-based normal ranges of enzymatic serum creatinine assessment [10]:

- 0 to 14 days: 0.92 mg/dL
- 15 days to <2 years: 0.36 mg/dL
- 2 to <5 years: 0.43 mg/dL
- 5 to <12 years: 0.61 mg/dL
- 12 to <15 years: 0.81 mg/dL
- 15 to <19 years: 0.84 mg/dL (females), 1.08 mg/dL (males)

ACR American College of Radiology, dL deciliter, eGFR estimated glomerular filtration rate, h hour, KDIGO Kidney Disease: Improving Global Outcomes, kg kilogram, L liter, m meter, min minute, mg milligram, mL milliliter

^a Severe GFR reduction is <30 mL/min per 1.73 m² if >2 years old or >2 standard deviations below age-/gender-/body-size-specific normative mean values if <2 years old, according to 2012 KDIGO criteria [7]

threatening anaphylactoid reactions to intravenous contrast media are very rare, particularly in children. Of note, many symptoms of physiological reactions to contrast media are indistinguishable from allergic-like reactions, including nausea and vomiting, and in rare extreme cases seizures, pulmonary edema and cardiopulmonary arrest [1].

A history of severe allergic-like reaction to an intravenous contrast media is the most relevant risk factor for recurrent reaction [1, 21, 22]. A history of asthma has been reported to increase the overall risk of a subsequent reaction by up to six times, although this risk might be negligible for patients with well-controlled asthma [23–27]. Notably, a history of asthma is not a contraindication for IBCM or GBCM use, and a history of asthma (including active asthma symptoms) is not a mandatory indication for premedication [1]. Generalized allergic tendencies, particularly those with a history of anaphylactic responses to one or more allergens, have also been reported to increase a person's risk of contrast reaction [28, 29], but a generalized history of allergies or atopy is not an indication for premedication or avoidance of IBCM or GBCM [1]. Despite these factors, identifying these particular risk factors prior to contrast media administration is considered mandatory by most surveyed pediatric radiologists [28].

Similar to children with shellfish or povidone-iodine (e.g., Betadine) allergies, children with a history of allergic-like reaction to GBCM are at no greater risk of allergic-like reaction to IBCM than a different child with a different non-contrast-media allergic response of similar severity [1, 30, 31]. However, skin-testing of adults with history of allergic-like reaction to a known intravenous IBCM agent has shown cross-reactivity to additional varieties of IBCM in some people, more commonly in those with severe reactions [32, 33]. Similar findings have been reported for both adults and children with intravenous GBCM allergy, including cross-reactivity between linear agents and macrocyclic agents [34, 35]. If an allergic-like reaction to contrast media has been identified, referral to an allergist can be considered case by case for further evaluation and possible skin testing.

Thyroid dysfunction

IBCM exposure has been associated with increased risk of thyroid dysfunction in children, most commonly hypothyroidism. This was described in a recent case-control study ($n=870$ cases of incident thyroid dysfunction from 2001 to 2015, mean case/control age of 8.4/7.3 years with standard deviation of 6.1/7.3, odds ratio 2.60, 95% confidence interval [CI] 1.43–4.72, $P<.01$) within a median (interquartile range) of 10.8 (6.6–17.9) months following administration [36]. A single intravenous IBCM bolus can contain approximately 150 times the recommended daily amount of iodine intake for children

1–8 years old [37, 38]. Thyroid dysfunction is thought to result from a failure to escape the acute Wolff-Chaikoff effect, wherein the thyroid gland responds to excess iodine exposure by temporarily reducing thyroid hormone production over 24–48 hours [39–42]. At present, the incidence and duration of thyroid dysfunction in children from IBCM exposure, as well as the clinical significance of these findings, are incompletely characterized. While the detrimental effects of untreated overt hypothyroidism to neurological development are well established [43, 44], effects of subclinical hypothyroidism in young children are less well understood [45]. Iodine-induced hyperthyroidism (the Jöed-Basedow phenomenon), more commonly reported in adults, might be caused by quiescent nodules that transition to hyperfunction when exposed to excess iodine levels, which can remain elevated for 4–8 weeks following IBCM administration [41, 46].

In 2015, the United States Food and Drug Administration (FDA) issued a safety announcement regarding 10 cases of underactive thyroid, reported between 1969 and 2012, in infants younger than 4 months who were diagnosed within a month of receiving IBCM [47]. In all reported cases, the infants were either premature or had serious underlying medical conditions. Some infants received treatment, and the effects were thought to be temporary. Nonetheless, health care professionals were advised to use clinical judgment to determine whether testing for hypothyroidism might be necessary in similar cases. Some practitioners have advocated that all children receiving IBCM be monitored for thyroid dysfunction for a year following exposure [36], but no consensus guidelines for this practice exist. High-risk pediatric subpopulations are not well characterized, and the benefits of such screening efforts have not been demonstrated. Although iodine-induced thyroid dysfunction can occur in any individual, it is most commonly reported in those with predisposing conditions, such as underlying thyroid disease and chronic or end-stage renal disease, because iodine is principally excreted via the kidneys [41, 42, 48]. For this reason, radiologists should consider screening pediatric patients for these conditions and, if present, contacting the referring clinician prior to the study to discuss the associated risks.

Pediatric patients with a history of thyroid cancer or Graves disease might undergo radioactive iodine-based imaging and therapy, and require additional consideration prior to administration of IBCM. Iodine uptake by thyroid tissue decreases approximately 1 week after IBCM administration and lasts for several weeks. If a radioactive iodine-based nuclear medicine study or treatment is planned for a pediatric patient following an IBCM-enhanced exam, a 2- to 3-month washout period between administrations is recommended [49, 50], and this recommendation should be discussed with the referring clinician prior to IBCM administration.

Post-contrast acute kidney injury and contrast-induced nephropathy

Contrast-induced nephropathy (CIN) is defined as an acute decrease in renal function within 48 hours of administration of contrast media that was *caused* by the administration. CIN is a subgroup of post-contrast acute kidney injury (AKI) [1]. Post-contrast AKI is a correlative diagnosis resulting from any cause during the same time interval. Two studies ($n=144$ and $n=233$) of pediatric inpatient and outpatient populations by Caintais et al. [51] and Zo'o et al. [52] found incidences of post-contrast AKI ranging 4–10% following intravenous administration of IBCM. Caintais et al. employed criteria suggested by the Acute Kidney Injury Network and the ACR to define acute kidney injury: (1) absolute serum creatinine increase ≥ 0.3 mg/dL, or (2) percentage increase in serum creatinine ≥ 1.5 -fold above baseline or (3) urine output reduced to ≤ 0.5 mL/kg/h for at least 6 hours [1, 51, 53]. However, a traditional or propensity-matched control group of people who did not receive contrast media was not included in either study, which limits the causal inference of the results because of the potential selection bias and background variation in serum creatinine within the population selected to undergo imaging [54, 55]. The incidence of CIN in children receiving intravenous contrast media could be significantly lower. In amalgam, the results from a group of recent studies that employed propensity-matching in adults suggested that CIN is likely real but exceptionally rare [56–60]. A recent study by Bedoya et al. [61] of neonates (age 0–30 days) who received either intravenous IBCM ($n=59$) or GBCM ($n=81$) found no evidence of CIN with either media compared to propensity-matched control groups that did not receive intravenous contrast media. Additional studies employing intravenous GBCM in children have shown similar results [62, 63], and GBCMs are not known to be nephrotoxic when used in the standard dose range. Of note, 9% of neonates in the IBCM recipient group of the study by Bedoya et al. had higher serum creatinine levels in the first 48 hours following contrast media administration, similar to the incidence of post-contrast AKI reported by Caintais et al. [51], but this proportion was not significantly different from the propensity-matched control group that did not receive IBCM.

In the Caintais et al. [51] study, post-contrast AKI and possibly CIN were associated with hospital readmission within 30 days in a cohort of pediatric patients with a wide range of baseline kidney function, nephrotoxic drug exposure and medical comorbidities (prematurity, chronic heart failure, chronic kidney disease, history of glomerulopathy; adjusted odds ratio 3.6, 95% CI 1.4–9.5). Other studies have similarly found associations between all-cause AKI and unfavorable outcomes in pediatric patients, but have also lacked appropriate control groups and subpopulation analysis to definitively establish causal inference between the administration of

intravenous contrast media and these outcomes [64–68]. At present, the clinical significance of CIN in children is uncertain.

Although there is no universally accepted threshold value for serum creatinine or calculated estimated glomerular filtration rate (eGFR) that contraindicates administration of intravenous IBCM or GBCM, some have advocated for specific thresholds to prompt a pre-administration clinical consult for people who might be particularly vulnerable to the small potential risks of intravenous contrast administration [60, 61, 69, 70]. These include children with known congenital abnormalities of the kidney and urinary tract (e.g., solitary kidney, renal hypoplasia/dysplasia, obstructive uropathy), other conditions causing chronic kidney disease (CKD), those at risk of developing CKD in the future (uncontrolled hypertension, diabetes mellitus) and children with AKI [71–73]. By asking multiple, targeted screening questions on this topic, clinicians can improve sensitivity in detecting children who might have baseline kidney disease, are theoretically at higher risk of CIN, and for whom the ACR recommends obtaining baseline renal function testing [1, 69, 70, 74]. Based on the literature, we propose conservative thresholds to identify potentially abnormal eGFR values in children based on age, as well as additional criteria for assessing pediatric renal function, in Table 4 [7–10, 61, 75, 76]. In many cases, particularly for children younger than 2 years, values outside of published normal ranges might be normal in the context of renal maturation. When the indication for intravenous contrast media is reasonable and laboratory values are abnormal in a child younger than 2 years, a nephrologist can be involved in the discussion to avoid unwarranted alterations in practice patterns. Oliguric patients on dialysis are theoretically at risk of converting to an anuric state if they experience CIN, and clinical consultation should be considered pre-contrast-administration in these children as well. There are no universally accepted time intervals for serum creatinine measurement prior to intravenous contrast administration — proposed intervals are presented in Table 3. In the absence of an abnormally large-volume contrast media bolus or significant accompanying cardiac dysfunction, there is no need for urgent dialysis after intravenous contrast media administration for these patients [77].

Metformin

Metformin has been shown to help achieve glycemic control in children 10–17 years of age with type 2 diabetes [78], and it is recommended by the American Diabetes Association as first-line therapy at the time of diagnosis for metabolically stable children and adolescents with eGFR >30 mL/min/1.73 m² [79]. Because of renal excretion of the drug and the risk of lactic acidosis if it accumulates, metformin is contraindicated in children with inadequate renal function. Most surveyed

pediatric radiologists considered assessing for use of metformin-containing drugs mandatory prior to IBCM administration [28]. Because of the small but likely real risk of CIN with intravenous IBCM exposure, metformin-containing medications should be stopped at the time of administration and held for 48 hours in children with AKI or advanced CKD (eGFR <30 mL/min per 1.73 m²) [1, 7]. Restoration of adequate renal function should be confirmed prior to re-initiating metformin therapy. We recommend discussing these risks and dosing schedule interruption with the referring physician of any pediatric patient taking metformin who also has a history or laboratory results suggesting co-existing acute or severe chronic kidney disease prior to administration of intravenous IBCM [28, 80, 81]. There is no need to stop the drug for children with normal renal function or only mild to moderate CKD. Provided appropriate, weight-based dosing of GBCM, it is not necessary to discontinue metformin following contrast administration [1].

Nephrogenic systemic fibrosis

Nephrogenic systemic fibrosis (NSF) is a rare fibrosing disease primarily involving the skin and subcutaneous tissue and potentially involving other organs. NSF is associated with intravenous GBCM exposure and is most common in people with severe renal compromise. Recent literature suggests that there has only been one case report of NSF in a patient with an eGFR above 30 mL/min/1.73 m², and no cases with an eGFR greater than 60 mL/min/1.73 m² [82, 83]. Macrocyclic gadolinium-based contrast media, employed at the majority of pediatric hospitals that responded to a recent survey [3], demonstrate few, if any, unconfounded cases of NSF [1]. Even prior to this survey, when linear gadolinium-based contrast media were more commonly administered to children, a meta-analysis published in 2014 found only 23 reported cases in children [84]. Of these 23 children, 6 had no documented exposure to GBCM. Of the 17 pediatric patients with NSF who had known exposure to GBCM, 12 received gadodiamide (Omniscan). There were no cases of NSF in children younger than 6 years. All children with available data had severe renal dysfunction. Nonetheless the ACR recommends similar preventative guidelines for children as for adults. Assuming administration of a group II macrocyclic GBCM (gadobenate dimeglumine, gadobutrol, gadoterate acid, and gadoteridol) and appropriate dosing (including, when absolutely necessary, multiple doses of GBCM in a relatively short time frame), any level of renal function is permissible, and thus screening renal function is now optional for these contrast media [1]. The very small potential risk of NSF should still be given attention in the risk/benefit consideration for children with known AKI and advanced CKD (eGFR <30 mL/min/1.73 m² in children >2 years old, or 2 standard

deviations below mean normative values specific to age, gender and body size for younger children) under consideration for administration of intravenous GBCM [6–8, 85, 86]. If the child is on dialysis, the ACR suggests that dialysis following group II GBCM administration might further reduce the risk of NSF, although this has not been scientifically proved [1].

Myasthenia gravis

A study by Somashekar et al. [87] of predominantly adult patients with myasthenia gravis showed an increased risk of acute myasthenia gravis symptom exacerbation following administration of IBCM compared to patients undergoing non-contrast CT examinations (6.3% or 7/112 patients versus 0.6% or 1/155 patients); however, patients with neonatal and congenital myasthenia gravis were excluded from this study because of the distinct pathophysiology of the disease in this patient cohort, and to our knowledge these results have not been reproduced in study of predominantly pediatric patients. The assessment of myasthenia gravis disease status was not viewed as mandatory in a survey of pediatric radiologists published in 2014 [28]. Further studies in pediatric populations are needed to better define the risk to pediatric patients with myasthenia gravis.

Prophylaxis

Prophylaxis for allergic-like reactions

A 2010 survey of practice patterns at many pediatric radiology practices in the United States and Canada revealed highly variable policies regarding premedication for prevention of allergic-like reactions to intravenous contrast media [2]. This likely reflects the limited pediatric-specific research on this topic, and the overall limitations of premedication regimens. Allergic-like reactions following premedication regimens can still occur in children, and the frequency of these “breakthrough” reactions is unknown [12, 88]. In several recent large ($n > 100$) and predominantly adult studies, breakthrough allergic-like reaction rates have been reported to occur in 1–34% of cases [88–92]. Mervak et al. [88] estimated that for patients with prior IBCM allergic-like reaction, the number needed to treat was 569 (95% CI 386–1,083) to prevent one severe reaction. Davenport et al. [93] found that for high-risk inpatients, even when using the most favorable modeling, administering a 13-hour prophylactic corticosteroid regimen resulted in three times more patient deaths, likely related to hospital-associated infections, than lives saved from lethal contrast media reactions. While unfortunate and unpredictable, even severe allergic reactions to contrast media are still treatable, and when treated appropriately, most of these cases

in adults have no long-term sequelae [94]. In addition to the delayed care and prolonged hospitalizations that can result from premedication [91], short-duration corticosteroid regimens pose further risks to children. A recent meta-analysis including 38 pediatric studies found that vomiting, behavioral changes and sleep disturbance were each seen in about 5% of patients treated; adrenal-axis suppression occurred in up to 81%; and abdominal pain, facial swelling and flushing, and infection (in one case resulting in death) occurred in approximately 1% [95]. For these reasons, the authors favor a more conservative approach when recommending premedication regimens for children. Table 2 provides a risk-stratification schema for determining appropriate prophylactic measures for allergic-like reactions to intravenous contrast media (see also Table 5 [4] for specific premedication regimens).

As discussed, asthma and atopic tendencies have been associated with allergic-like reactions to contrast media and are commonly cited in isolation as rationale for administering prophylactic steroid regimens prior to intravenous contrast media administration [28, 29]. However the practice of premedication is not routine when other drugs such as antibiotics are administered to these children. Rather, preventive strategies are generally targeted at specific, known allergens. This, in combination with the variable efficacy and potential toxicity of corticosteroid therapy in children, has motivated the authors to recommend premedication with corticosteroid regimens only to children with a history of an allergic-like reaction, of any severity, to the same class of intravenous contrast media. Although the authors think that premedication is not mandatory for the administration of IBCM and GBCM in children with active symptoms of asthma or multiple moderate to severe allergies, these children should still probably undergo contrast-enhanced exams in facilities where a code team is available, such as a hospital setting.

Example premedication regimens, adapted from adult regimens, are presented in Table 5 [24, 91, 96–103]. For high-risk patients with no reasonable alternative but to receive the same

class of contrast media that elicited a prior severe reaction, administering a different medium within the same class, in addition to premedication, might help to reduce the likelihood of subsequent reaction [104, 105]. In the case of a child at high risk for reaction to a GBCM who needs a contrast-enhanced MRI exam, administration of a non-GBCM, such as ferumoxytol, can also be considered, although this agent also carries a risk of anaphylactic response and should not be administered to children with a history of allergic reaction to any intravenous iron replacement product [82, 106–108].

Prophylaxis for contrast-induced nephropathy

The efficacy of CIN prevention strategies has not been well studied in pediatric populations and current practices are based on data from adult populations. Until recently the general consensus for prophylactic intervention in high-risk patients has been intravascular volume expansion with isotonic saline, with some advocating for lactated ringers or half normal saline with added sodium bicarbonate to provide adequate osmolality without excessive chloride that might be associated with worse renal outcomes [1, 109–117]. However, studies supporting this practice generally did not include a non-intervention control arm. A recent large ($n=660$), randomized, open-label phase 3 study found no prophylactic intervention to be non-inferior to intravenous hydration with normal saline (3–4 mL/kg per hour for 4–12 hours before and 4–12 hours after the study) for prevention of CIN in high-risk adults (eGFR 30–59 mL/min/1.74 m²) [118]. Based on this body of adult literature, children with advanced CKD (e.g., eGFR <30 in children 2 years and older or eGFR >2 standard deviations below the age-, gender- and body-size-specific mean for children younger than 2 years [7]) who must undergo an IBCM-enhanced examination might benefit from CIN prophylaxis with intravascular volume expansion. The potential benefit can be discussed with the referring clinician, who is in the best position to determine the appropriateness of this

Table 5 Pediatric (<50 kg) premedication regimens

Outpatients and non-urgent cases	Dosage	Timing
Prednisone	0.5–0.7 mg/kg PO (up to 50 mg)	13 hours, 7 hours, and 1 hour prior to contrast administration
Diphenhydramine ^a	1.25 mg/kg PO (up to 50 mg)	1 hour prior to contrast administration
Emergency room patients, inpatients, and medically urgent outpatients		
Hydrocortisone	2 mg/kg IV (up to 200 mg)	5 hours and 1 hour prior to contrast administration
Diphenhydramine ^a	1.25 mg/kg IV or PO (up to 50 mg)	1 hour prior to contrast administration

IV intravenous, kg kilograms, mg milligrams, PO by mouth

^a For children with a history of mild allergic-like reaction to the same class of contrast media, a diphenhydramine-only regimen might be considered, although the risks and benefits conferred in this context have not been studied in pediatric patients [4]. In these instances, a code team should still be available to appropriately manage a more severe reaction

Diphenhydramine can be an optional component of the premedication protocol. Diphenhydramine can cause drowsiness, which in turn can theoretically obscure central nervous system symptoms of a more severe reaction, delaying administration of epinephrine

intervention and volume of the bolus based on the child's fluid status. In the high-CIN-risk adult population, intravenous hydration alone can lead to acute complications in up to 6% of patients (e.g., symptomatic heart failure, hyponatremia, arrhythmia) [118], and this risk might outweigh the potential prophylactic benefit if there is no reasonable alternative to performing an IBCM-enhanced examination in a child with severe kidney disease. Both sodium bicarbonate and N-acetylcysteine have insufficient evidence of efficacy for prophylaxis of CIN [115, 119].

Physiological reactions

Physiological reactions to intravenous contrast media administration, typically involving nausea, vomiting, warmth at the injection site and anxiety, are relatively common and of increased significance in children, who might move or cry in response, degrading image quality [120]. These effects are distinct from allergic-like reactions and are likely caused by direct chemotoxicity, osmototoxicity and molecular binding actions of the contrast media [121–125]. In the era of predominant use of low-osmolality iodinated contrast media, no specific prophylactic treatments are required for these transient reactions beyond appropriate contrast media dosing. If a child is old enough to converse, the likelihood of achieving diagnostic exam quality is improved by counseling the child about these common potential responses before the contrast medium is administered.

At the authors' institutions, we do not routinely require any duration of preparative fluid or solid food fasting for children prior to the administration of intravenous iodine-based or gadolinium-based contrast media unless the exam requires sedation. For sedated exams, the feeding instructions are generally related to the sedation regimen and not the administration of intravenous contrast media. Lee et al. [126] provided a systematic literature review that demonstrates little evidence to support the necessity of fluid fasting for the prevention of aspiration pneumonia in people receiving intravenous contrast-enhanced CT examinations. The authors suggested that patients be allowed to drink clear fluids such as water, tea or decaffeinated black coffee either without restriction or until at least 1 hour (gastric emptying of 90%) prior to contrast-enhanced CT [126].

Contrast media administration

Intravenous contrast media injection rates for routine (e.g., non-CT angiography) CT and MRI examinations in children typically range 1.0–2.0 mL/s [28, 127, 128]. For CT angiography exams, most pediatric radiologists in one survey elected to inject at a rate of 2.0–3.0 mL/s, although injection rates can

range up to 5.0 mL/s, particularly for larger children [28]. The gauge of the angiocatheter, which is commonly smaller for children than for adults, limits the maximum recommended injection rate (Table 6) [28]. Angiocatheters used for cross-sectional imaging most commonly range from 24-gauge (G) to 20 G, and occasionally 18 G for specific indications. Twenty-four-gauge catheters are typically used for children under 11.5 kg, and 18-G catheters are reserved for arteriograms in larger children (e.g., >55 kg) who require very high flow rates. Notably, the vast majority of contrast-enhanced cross-sectional imaging studies can be performed at injection rates less than 5.0 mL/s using angiocatheter sizes as small as 24 G. Relatively small overall volumes of contrast media are typically administered intravenously to infants and newborns, on the order of 2 mL/kg for IBCM [2] and 0.2 mL/kg for GBCM [128]. This volume, as well as the volume of associated saline flushes, can be adjusted in the context of fluid restriction (e.g., cardiac and renal patients) [28].

When access is considered tenuous, hand injection of contrast media might be performed rather than power injection to minimize the risk of vessel injury and extravasation [1, 28, 129]. Small 3- to 4-French (Fr) peripherally inserted central catheters (PICC) used in children under 15 kg, and 24-G angiocatheters used in children <11.5 kg, are also typically hand-injected because of the small volume of contrast media typically administered to these children. However, whenever possible power injector is the preferred method of injection to minimize radiation exposure to technologists and nurses and to more precisely control injection pressure and flow rates. It is important to verify appropriate tip position, ease of injection (via saline flush), any history of catheter repair, and power injector compatibility of both implanted and non-implanted central venous catheters in pediatric patients prior to use for this purpose. Lozano et al. [130] found in a series of 78 PICC power injections of contrast media for CT in adults that 62.5% of catheters terminating above the lower third of the superior vena cava (SVC) were displaced after the injection, versus 10.1% of those positioned within the lower third of the SVC. Some manufacturers of central venous lines and

Table 6 Maximum recommended intravenous contrast media injection rates for pediatric angiocatheters

Maximum injection rate (mL/s)	Catheter size (gauge)
5.0	16–18
4.0	20
2.5	22
1.0	24

Adapted from Callahan et al. [28]. Injection of catheter gauges 16–22 is typically performed with a power injector. The small volume of contrast media typically delivered via 24-gauge catheter is usually injected by hand

mL milliliter, s second

PICCs suggest that the catheter tip be located above the right atrium and within the lower third of the SVC prior to power injection of contrast media [131]. Improperly positioned, clogged, previously repaired or non-compatible catheters are also theoretically at risk of damage with rapid contrast media administration, including with hand injections [132, 133]. PICCs smaller than 3 Fr, dialysis lines, and catheters placed in scalp veins or umbilical veins are not commonly utilized for injecting contrast media in the context of cross-sectional imaging.

Treatment of adverse and allergic-like reactions

In general, close observation of infants and children is required during and immediately following the administration of intravenous contrast media to assess for adverse reactions because many of these children cannot verbalize their symptoms. The approach to treatment of acute contrast media reactions in children, as recommended by the ACR, the Joint Task Force on Practice Parameters for allergists and immunologists, and the National Institute of Allergy and Infectious Diseases, is summarized in Table 7 [1, 134, 135].

Diphenhydramine (Benadryl) is a nonselective antihistamine that can be administered orally, intravenously or less commonly intramuscularly (Table 7). It is commonly used to treat cutaneous reactions, including moderate to severe pruritus and urticaria. Diphenhydramine does not effectively treat more severe anaphylactoid reactions including bronchospasm, laryngeal edema or hypovolemic shock, and can result in drowsiness and hypotension.

Albuterol is a beta-agonist and is typically inhaled via a metered dose inhaler or nebulizer (Table 7). Albuterol is a bronchodilator that is used to treat bronchospasm. Like diphenhydramine, albuterol does not effectively treat more severe anaphylactoid reactions such as laryngeal edema or hypovolemic shock. Supplemental oxygen should also be considered to treat respiratory symptoms related to adverse reactions to intravenous contrast media (Table 7).

Epinephrine is both an alpha- and beta-agonist and is the first-line treatment of any severe allergic-like or anaphylactoid reaction to intravenous contrast media. Children on a beta-blocker therapy might be refractory to epinephrine, and in these cases glucagon might have a role in treating anaphylactoid reaction. Epinephrine is typically administered intramuscularly for treating anaphylactoid reaction. It is the authors' opinion that the easiest method to administer epinephrine intramuscularly is via autoinjector. These devices are designed to be compressed against the anterolateral thigh for 2–10 seconds, during which a needle extends through the skin and delivers a fixed dose of epinephrine. Repeated dose of epinephrine can be administered every 5–15 minutes if signs and

symptoms of anaphylactoid reaction persist. The FDA has approved specific devices for specific body weight classes starting at 7.5 kilograms (16.5 pounds), as detailed in Table 7. Below 7.5 kilograms (16.5 pounds) of body weight, there are no FDA-approved devices, and weight-based epinephrine doses should be manually prepared for administration in these cases. However, junior doses (0.1 mg or 0.15 mg) of epinephrine autoinjectors can be considered if no alternative is rapidly available. While the speed and ease of use that autoinjectors provide make them a facile tool in an emergency, they are relatively expensive, must be regularly replaced when expired, and require device-specific training for safe use in children. In particular, it is important to ensure that the child's thigh is appropriately restrained and immobilized during the 2–10 seconds that an autoinjector is compressed against the child's body. Autoinjector devices have variable mechanisms of both epinephrine injection and needle self-retraction. The needle in some models remains fully extended for the entire time the device is compressed against the thigh. If a child's leg is not appropriately immobilized, the child is likely to move in response to the pain of the puncture and injection, and this could bend the needle in the skin, lacerate the skin, or interrupt body contact with the device, leading to uncertainty regarding dose delivery and use of an additional autoinjector device [136].

Extravasation

Soft-tissue extravasation of intravenous contrast media occurs in approximately 0.3% of pediatric patients when a power injector is used for delivery [137]. For non-verbal infants and children, special attention should be paid to the injection site to assess for this complication. Direct palpation of catheter venipuncture site during the initial seconds of the injection is particularly effective for detecting extravasation [23]; in these cases, the injection can be stopped immediately to limit the extravasated volume. If an extravasation is identified, the child should be monitored until the supervising radiologist has sufficiently assessed for potential evolution of symptoms over time. Children might be asymptomatic or develop swelling, tightness, stinging/burning pain, edema, erythema or tenderness at the injection site [138]. Initial treatment typically involves elevating the affected extremity or injection site and applying warm or cold compresses [28, 139]. In most cases the extravasation is mild in severity and resolves following conservative treatment with minimal or no adverse effects [140]. Surgical consultation is reserved for rare cases with progressive pain or swelling, decreased capillary refill or change in sensation (e.g., paresthesia), all of which could indicate compartment syndrome, skin blistering or ulceration [141].

Table 7 Treatment of acute contrast reactions in children

Symptom	Treatment ^a
Urticaria	Consider diphenhydramine^b in more widespread/progressive cases at 1 mg/kg PO or IV (slowly over 1–2 min) up to max dose 50 mg
Bronchospasm	Oxygen by mask (6–10 L/min) β-2 agonist metered dose inhaler (e.g., Albuterol) 2 puffs (90 mcg per puff) every 20–30 min as needed up to 3 times. A nebulizer could also be used Epinephrine^c IM
Laryngeal edema	Oxygen by mask (6–10 L/min) Epinephrine^c IM
Hypotension	Elevate the patient's legs to at least 60° Oxygen by mask (6–10 L/min) IV 0.9% normal saline or lactated ringers 10–20 mL/kg wide open up to 500–1,000 mL max Epinephrine^c IM - If no response to above measures - Bradycardia: Atropine IV 0.2 mL/kg of 0.1 mg/mL solution (0.02 mg/kg) into a running IV infusion of fluids, minimum single dose = 0.1 mg, max single dose = 1.0 mg, max total dose = 1.0 mg for children ≤12 years old and 2.0 mg for >12 years old. - Tachycardia: Epinephrine^c IV (if no IV access, can give IM)
Seizures/convulsions	Turn patient on side to avoid aspiration Suction airway as needed Oxygen by mask (6–10 L/min)

FDA U. S. Food and Drug Administration, IV intravenous, kg kilograms, L liters, max maximum, mcg micrograms, min minutes, mg milligrams, PO by mouth, μg micrograms

^a All patients should be observed until symptoms are resolving (longer if treatment is received), with vitals monitored, and IV access preserved. At the authors' institutions, for all cases requiring treatment with more than just diphenhydramine, or with symptoms persistent or worsening, an emergency response team is called immediately. For patients who do not immediately respond to symptoms requiring treatment with epinephrine or β-2 agonist, consider transfer to the emergency department

^b Diphenhydramine can cause drowsiness, which can theoretically obscure central nervous system symptoms of a more severe reaction, delaying administration of epinephrine. IV delivery can also cause or worsen hypotension

^c Pediatric epinephrine dosing:

- Intramuscular (IM)**
 - 0.01 mL/kg of 1:1,000 dilution (0.01 mg/kg) up to max 0.3 mL (0.3 mg) for single dose, can repeat every 5–15 min
 - Auto-injectors FDA approved by patient weight class
 - 7.5–15 kg (16.5–33 pounds): infant/toddler epinephrine auto-injector (Auvi-Q only — lavender color), 0.1 mg
 - 15–25 kg (33–55 pounds): pediatric epinephrine auto-injector (Auvi Q, EpiPen Jr or generic autoinjector) 0.15 mg
 - ≥25 kg (55 pounds): adult epinephrine auto-injector (Auvi Q, EpiPen Jr or generic autoinjector) 0.3 mg. Note that although product labeling often states 30 kg as the minimum weight for 0.3 mg dosage, recent practice guidelines recommend using 25 kg as the threshold [134]
- Intravenous (IV)**
 - 0.1 mL/kg of 1:10,000 dilution (0.01 mg/kg) administered slowly into a running IV infusion of fluids up to max 1.0 mL (0.1 mg) for a single dose, can repeat every 5–15 min up to 1 mg total dose
 - Increased risk of arrhythmias, cardiac monitoring should be in place

Conclusion

The administration of intravenous contrast media in children is a nuanced task, with a few general concepts that should be familiar to all practicing radiologists. By employing targeted screening questions to identify high-risk pediatric patients prior to contrast media administration and consulting with

referring clinicians regarding alternative imaging options or premedication in appropriate cases, IBCM and GBCM can generally be administered with excellent patient tolerance. In the rare event of an acute adverse reaction or contrast media extravasation, treatment using pediatric-specific drug dosages resolves the complication over a short period of time without long-term sequelae in the vast majority of cases.

Acknowledgments Dr. Maloney is supported in part through a National Institutes of Health, National Research Service Award training grant (grant number 2 T32 DK00742).

Compliance with ethical standards

Conflicts of interest None

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