CONTRAST MEDIA IN CHILDREN

Principles regarding contrast media utilization and associated adverse events are generally similar between children and adults. This section will address specific areas in which pediatric use of contrast material differs from adult use and attempt to avoid repeating recommendations that are similar for both patient populations.

Iodinated Intravascular Contrast Media

Unique Considerations in Children

Contrast Agent Osmolality

Osmolality is an important physical property of contrast media. A variety of the adverse effects attributed to intravascularly administered iodinated contrast agents seem to be related, at least in part, to this physical property, including physiologic side effects, allergic-like reactions, complications following contrast medium extravasation, and fluid shifts. There is noteworthy variation in the osmolality of the various nonionic iodinated contrast agents approved for use in the United States with equivalent iodine concentrations (see Appendix A).

Contrast media osmolality is of particular importance in neonates and small children. These patients are thought to be especially susceptible to fluid shifts and have a lower tolerance for intravascular (IV) osmotic loads when compared to adults. IV administration of a hyperosmolality contrast medium may theoretically result in migration of fluid from extravascular soft tissues into blood vessels, consequently expanding blood volume. If the fluid shift is large, cardiac failure and pulmonary edema can result. In children with significant pre-existing cardiac dysfunction, consideration should be given to the use of an iso-osmolality intravascular contrast agent.

Contrast Media Viscosity

Viscosity, a measure of fluid resistance to stress, is another important physical property of contrast media. As viscosity increases, the pressure associated with IV contrast medium injection increases. This physical property is especially important for pediatric patients due to the use of small gauge angiocatheters in tiny blood vessels. Contrast medium viscosity and angiocatheter size are important factors in determining maximum injection rates. If a rapid injection rate is desired through a small angiocatheter and contrast medium viscosity is high, two problems can potentially result. First, the desired injection flow rate may not be achieved. Second, high pressure may cause catheter failure and vessel injury. There is distinct variation in viscosity between different contrast agents (see Appendix A). Additionally, contrast medium viscosity is not directly proportional to the concentration of iodine. Using iopamidol (Isovue) as an example, at body temperature, viscosity increases from 2.0 centipoise (cps) at 200 mg/ml to 9.4 cps at 370 mg/ml at body temperature.

Viscosity of contrast media is affected by temperature (see Appendix A). As temperature increases, viscosity decreases allowing for increased flow rates at lower pressures. A study by Vergara and Seguel [1] that included both adult and pediatric patients showed that warming contrast media resulted in fewer adverse events following injection when compared to contrast media administered at room temperature.

Other Unique Issues in Children

Several additional issues complicate the administration of IV contrast media to neonates and children, including the use of small volumes of contrast medium, the use of small gauge angiocatheters, and unusual vascular access sites. First, very small volumes of contrast media are typically administered to neonates and infants (typically 2 ml/kg). As a result, timing of image acquisition with regard to contrast medium administration may be important when performing certain imaging studies, such as computed tomography (CT) angiography. A slower injection rate (compared to that used in older children and adults) may be useful to prolong IV enhancement. Second, small gauge angiocatheters (for example, 24-gauge) located in tiny peripheral veins (for example, in the hand or foot) are commonly utilized in neonates and infants. A study by Amaral et al [2] showed that 24-gauge angiocatheters in a peripheral location can be safely power injected using a maximum flow rate of approximately 1.5 ml/sec and a maximum pressure of 150 pounds per square inch (psi). When access is thought to be tenuous, hand injection of contrast medium should be strongly considered in order to minimize risk of vessel injury and extravasation. As many currently used central venous catheters are not approved for power injection, one should always verify that the catheter is approved for such injection and that the pressure used does not exceed its rating. Particular attention should be paid to the injection sites of neonates and infants as such individuals cannot effectively communicate the possibility of an injection site complication. Extravasation rates in children appear to be similar to those of the adult population. An extravasation rate of 0.3% was documented in a study of 554 children in which a power injector was used to administer iodinated contrast medium [2]. Most extravasations in the pediatric population resolve without untoward sequelae. A study by Wang et al [3] showed that 15 of 17 cases of contrast medium extravasation in children were mild in severity with minimal or no adverse effects.

Physiologic Side Effects in Children

While most minor physiologic side effects to IV contrast medium administration in adults are of minimal significance, such events are often of increased importance in children [4]. For example, local warmth at the injection site and nausea, generally regarded to be physiologic side effects to contrast medium administration, may cause a child to move or cry. Such a response to contrast medium injection may result in the acquisition of a nondiagnostic imaging study necessitating repeat imaging and additional exposure to contrast medium and radiation. There may be differences between the various nonionic low-osmolality iodinated contrast agents with regard to the incidence of injection-related side-effects [4].

Incidence of Allergic-Like Reactions

There are several difficulties in interpreting the available literature on the incidence of allergic-like reactions to IV iodinated contrast media in children. First, there are no standard definitions for such reactions. For example, many studies fail to discriminate between physiologic side effects and allergic-like reactions. In addition, these studies lack agreement on what constitutes mild, moderate, or severe reactions. Second, there is a lack of controlled prospective pediatric studies on the topic. Such investigations are difficult to perform as allergic-like reactions to contrast media in children are rare and large numbers of patients would be needed to acquire statistically meaningful results. Much of the existing literature is retrospective in nature, for which it is impossible to ensure that all adverse reactions are appropriately documented.

Therefore, not surprisingly, the reported incidence of pediatric allergic-like reactions to contrast media is variable, at least in part due to the factors mentioned above. It is generally agreed, however, that the incidence of allergic-like reactions in children is lower than that in adults [1,5]. A very large study by Katayama et al [6], when stratified by age and the use of nonionic iodinated contrast media, showed that patients less than 10 years of age and the elderly have the lowest rates of adverse reactions. A study by Dillman et al [5] retrospectively reviewed greater than 11,000 IV injections of low-osmolality nonionic iodinated contrast media and documented an allergic-like reaction rate of 0.18%. Of the 20 reactions documented in their study, 16 were mild, one was moderate, and three were severe [5]. A similarly performed study in adult patients from the same institution over a similar time period revealed an adult reaction rate of approximately 0.6% [7]. A study by Callahan et al. of 12,494 consecutive patients up to 21 years of age revealed 0.46% incidence of adverse reactions to ioversol, the majority of which were mild [8]. A smaller study by Fjelldal et al [9] documented 5 allergic-like reactions to iohexol following a total of 547 injections, for a rate of reaction of 0.9%. While fatal reactions to contrast media in children are extremely rare (and may be due to co-morbid conditions in some cases), infants and young children require close observation during and following IV contrast medium administration as they are unable to verbalize reaction-related discomfort or symptoms.

Prevention of Allergic-Like Reactions

General guidelines for the prevention of allergic-like reactions in children are similar to those used for adult patients. A sample pediatric premedication regimen, using a combination of corticosteroid and antihistamine, is described in the Table A at the end of this chapter. Allergic-like reactions following premedication may still occur, although the frequency of such reactions is unknown [5].

Treatment of Allergic-Like Reactions

General guidelines for the treatment of allergic-like reactions in children are similar to those used for adult patients. Pediatric medication dosages, however, may be significantly different from adult dosages used in the management of such reactions (Table 5). It is recommended that a pediatric medication chart with weight-based dosages be placed on the emergency cart or posted in the room wherever intravascular contrast media is to be injected into children. Dedicated pediatric emergency resuscitation equipment (including various sizes of emergency airway devices and supplemental oxygen facemasks) also should be available in all such locations (Table 7). A separate box of pediatric airway equipment attached to the emergency cart may be useful in areas where both children and adults receive contrast media.

Contrast-Induced Nephrotoxicity (CIN) in Children

There has been no large prospective investigation dealing with the possible nephrotoxic effects of IV low-osmolality iodinated contrast agents in children. Consequently, the effects of contrast media on the kidneys are generally assumed to be similar between children and adults. A few key differences are discussed below.

Measurement of Renal Function in Children

Serum creatinine concentration reflects the balance between creatinine production and excretion. Creatinine is a break-down product of skeletal muscle, and its rate of production is proportional to muscle mass. Muscle mass depends on a variety of factors, including patient age, gender, and level of physical activity. Normal serum creatinine concentrations, thus, are quite variable in pediatric patients, even in the presence of preserved renal function. It is important to recognize that normal adult creatinine concentrations cannot be applied to the pediatric population. Normal pediatric serum creatinine concentrations increase with age, with the upper limits of normal always less than adult values (note: age-based normal serum creatinine concentrations also may vary slightly from laboratory to laboratory).

There are problems with using serum creatinine concentration as the sole marker of renal function. First, a normal serum creatinine value does not mean that renal function is preserved. For example, an increase in creatinine from 0.4 mg/dl to 0.8 mg/ml in a 10-year old patient would be clinically significant and suggest some degree of renal impairment, even though both measurements may be within acceptable limits for patient age. Serum creatinine concentration may not become abnormal until glomerular filtration has decreased substantially. Second, it may take several days in the setting of acute renal failure for serum creatinine concentration to rise. A patient, therefore, may have impaired renal function and a normal serum creatinine concentration.

Measurement of blood urea nitrogen (BUN) concentration is a poor indicator of renal function. BUN concentration depends on numerous variables in addition to renal function, including daily dietary protein intake, hepatic function, and patient hydration.

A popular manner by which to express renal function in children is estimated glomerular filtration rate (eGFR). It is important to note that the two formulae used to calculate pediatric eGFR (see below) are different from those used in adults. eGFR calculations in children require knowledge of patient serum creatinine concentration and height. In addition, the assay used to measure serum creatinine concentration must be known.

GFR Calculators for Children

There is no perfect manner of estimating the GFR in children. The National Kidney Disease Education Program (NKDEP) (an initiative of the National Institutes of Health (NIH)) has published the following information regarding the estimation of GFR in children (http://nkdep.nih.gov/professionals/gfr_calculators/gfr_children.htm):

Currently, the best equation for estimating GFR from serum creatinine in children is the Schwartz equation.

There are several laboratory methods of measuring serum creatinine concentration. These different methods give different results. At this time, it is recommended not to estimate GFR for children when using an alkaline picrate ("Jaffe") method that has calibration traceable to isotope dilution mass spectrometry (IDMS).

Equation #1: Original Schwartz Equation (for use with routine creatinine methods that have not been recalibrated to be traceable to IDMS) [10]

GFR (mL/min/1.73 m^2) = (k x height) / serum creatinine concentration

- K = constant
  - K = 0.33 in premature infants
  - K = 0.45 in term infants to 1 year of age
  - K = 0.55 in children to 13 years of age
  - K = 0.70 in adolescent males (not females because of the presumed increase in male muscle mass, the constant remains 0.55 for females)
- Height in cm
- Serum creatinine in mg/dL

For this formula, the NKDEP presently recommends reporting estimated GFR values *greater than or equal to 75 mL/min/1.73 m^2* simply as "≥75 mL/min/1.73 m^2", not an exact number.

Equation #2: Interim IDMS-traceable Schwartz GFR calculator for children (for use with enzymatic creatinine methods that have been calibrated to be traceable to IDMS) [11]

GFR (mL/min/1.73 m2) = (0.41 x height) / serum creatinine

- Height in cm
- Serum creatinine in mg/mL

Prevention of CIN in At-Risk Children

Risk factors for CIN in children are thought to be similar to those in adults. Unfortunately, there are no established evidence-based guidelines for the prevention of CIN in children with impaired renal function. As no pediatric-specific measures for the prevention of CIN have been established in the literature, strategies described for use in adults should be considered when using IV iodinated contrast media in children with renal dysfunction. A noncontrast imaging examination should be performed if the clinical question can be answered without IV iodinated contrast media. In addition, the use of alternative imaging modalities, such as ultrasound and magnetic resonance imaging (with or without gadolinium-based contrast medium, depending on exact degree of renal impairment and the clinical question to be answered), should be considered.

Gadolinium-Based Intravascular Contrast Agents

There are only a few published studies that address adverse reactions to IV gadolinium-based contrast media in children. The guidelines for IV use of gadolinium-based contrast agents are generally similar in both the pediatric and adult populations. There are currently six gadolinium-based contrast agents approved for IV use in the United States. These agents are commonly used “off-label” in children as several of these agents are not approved for use in pediatric patients and no agent is approved for administration to individuals less than two years of age. A few pediatric-specific issues regarding these contrast agents are discussed below.

Osmolality and Viscosity

As with iodinated contrast media, there is a significant range in osmolality and viscosity of gadolinium-based MR contrast agents. Osmolality of gadolinium-based contrast media ranges from approximately 630 mosm/kg H_2O for gadoteridol (Prohance) to 1,970 mosm/kg H_2O for gadobenate dimeglumine (Multihance). Viscosities (at 37 degrees Celsius) range from 1.3 cps for gadoteridol (Prohance) to 5.3 cps for gadobenate dimeglumine (Multihance). These physical properties, however, are less important when using gadolinium-based contrast agents in children compared to iodinated contrast agents. The much smaller volumes of gadolinium-based contrast agents that are typically administered to pediatric patients’ likely result in only minimal fluid shifts. The slower injection flow rates generally used for gadolinium-based contrast agents result in lower injection-related pressures and decreased risk for vessel injury and extravasation.

Allergic-Like Reactions and Other Adverse Events

While rare, allergic-like reactions to intravascular gadolinium-based contrast media in children do occur. A study by Dillman et al [12] documented a 0.04% allergic-like reaction rate to these contrast agents in children. While mild reactions are most common, more significant reactions that require urgent medical management may occur [12]. Pediatric allergic-like reactions to gadolinium-based contrast media are treated similarly to those reactions to iodinated contrast agents (Table 5). A variety of physiologic side effects may also occur following administration of gadolinium-based contrast media, including coldness at the injection site; nausea, headache, and dizziness (see package inserts). There is no evidence for pediatric renal toxicity from gadolinium-based contrast media at approved doses. Extravasation of gadolinium-based contrast media is usually of minimal clinical significance because of the small volumes injected.

Nephrogenic Systemic Fibrosis (NSF) and Gadolinium-Based Contrast Media

There are only a small number of reported case of NSF in children (fewer than 10 as of 2008), the majority of which were described prior to this condition’s known apparent association with gadolinium-based contrast agents [13-19]. The youngest reported affected pediatric patient is 8 years of age [20], and all reported pediatric patients had significant renal dysfunction. As there are no evidence-based guidelines for the prevention of NSF in children, we recommend that adult guidelines for identifying at-risk patients and administering gadolinium-based contrast media in the presence of impaired renal function be followed. While there has been no reported case of NSF in a very young child, caution should be used when administering these contrast agents to preterm neonates and infants [20] due to renal immaturity and potential glomerular filtration rates under 30 $ml/min/1.73m^2$ [21].

Gastrointestinal Contrast Media

The most commonly used gastrointestinal contrast agents in children are barium-based. These agents can be administered by mouth, rectum, ostomy, or catheter residing in the gastrointestinal tract. These contrast agents are generally contraindicated in patients with suspected or known gastrointestinal tract perforation.

Iodinated contrast agents are usually preferred in the setting of suspected gastrointestinal tract perforation. As with IV iodinated contrast agents, osmolality should be considered when deciding which iodinated contrast agent to administer orally due to significant variability. Hyperosmolality iodinated contrast agents within the gastrointestinal tract may cause fluid shifts between bowel wall and lumen and, once absorbed, between extravascular soft tissues and blood vessels [22]. Neonates and older children with cardiac and renal impairment may be most susceptible to such fluid shifts. In such patients, low-osmolality or iso-osmolality contrast agents should be considered for imaging of the upper gastrointestinal tract. Regarding rectal use, higher osmolality contrast agents can usually be diluted to a lower osmolality and still have sufficient iodine concentration to allow diagnostic imaging. High-osmolality iodinated contrast agents should also be avoided in children who are at risk for aspiration. Aspirated hyperosmolality contrast medium may cause fluid shifts at the alveolar level and chemical pneumonitis with resultant pulmonary edema [23,24]. Aspiration of large volumes of both barium-based and iodinated oral contrast agents rarely may be fatal [24].

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Table A

Sample Pediatric Corticosteriod and Antihistamine Premedication Regimen

	Dosage	**Timing**
Prednisone	0.5-0.7 mg/kg PO (up to 50 mg)	13, 7, and 1 hrs prior to contrast injection
Diphenhydramine	1.25 mg/kg PO (up to 50 mg)	1 hr prior to contrast injection

Note: Appropriate intravenous doses may be substituted for patients who cannot ingest PO medication.