

Clinical Applications of Gadopiclenol in Pediatric MRI

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Introduction

Gadolinium-based contrast agents (GBCAs) have been a mainstay in contrast-enhanced magnetic resonance imaging (MRI) for over 30 years owing to their ability to improve the diagnostic value of examinations.¹ Their broad utility is evident in their diverse indications, including lesion detection and characterization, cancer staging, delineating vasculature and associated diseases, and assessing infection and inflammation.²

Although GBCAs have a favorable safety profile and are used routinely across MRI indications, recent concerns have led to the voluntary marketing suspension of the less stable agents—gadopentetate dimeglumine (Magnevist), gadodiamide (Omniscan), and gadoversetamide (OptiMARK).³ Given that pediatric patients, in particular, may receive multiple doses over their lifetime, the careful selection and prudent use of GBCAs are paramount to optimizing diagnostic efficacy and ensuring patient safety for this

group.² This paper reviews considerations for selecting and utilizing GBCAs in pediatric MRI, focusing in particular on the new macrocyclic agent, gadopiclenol.

GBCAs: A Historical Perspective

Since its introduction in the 1980s, MRI has become an indispensable tool for diagnostic imaging, accelerated by the development of GBCAs.¹ Current estimates suggest that GBCAs are used in 30% to 45% of the approximately

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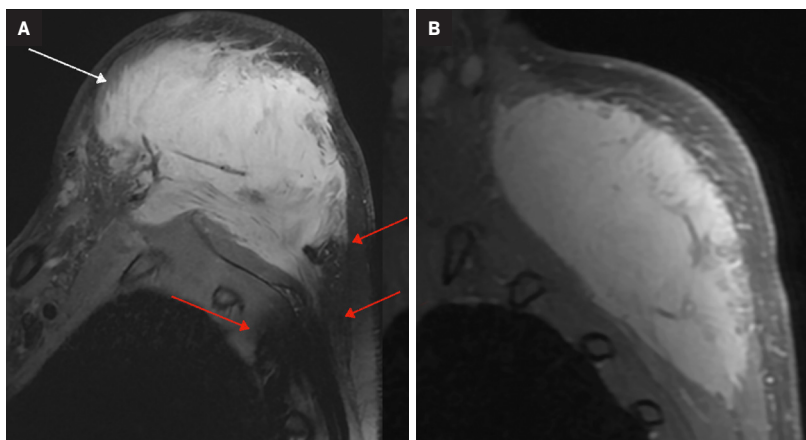
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Table 1. Properties of US Food and Drug Administration-approved Gadolinium-based Contrast Agents.⁵⁻¹⁵

| | LINEAR | | MACROCYCLIC | | | |
|-------------------------|--|------------------------------|--|--------------------------|---|---|
| Generic name (brand) | Gadobenate dimeglumine (MultiHance) | Gadoxetate disodium (Eovist) | Gadoteridol (ProHance) | Gadobutrol (Gadavist) | Gadoterate meglumine (Dotarem/Clariscan)* | Gadopiclenol (Vueway/Elucirem) [†] |
| Manufacturer | Bracco Diagnostics | Bayer Healthcare | Bracco Diagnostics | Bayer Healthcare | Guerbet/ GE Healthcare | Bracco Diagnostics/ Guerbet |
| Ionicity | Ionic | Ionic | Nonionic | Nonionic | Ionic | Nonionic |
| Relaxivity at 1.5T/3.0T | 6.20/5.37 | 7.24/5.45 | 4.39/3.46 | 4.61/4.46 | 3.91/3.43 | 12.8/11.6 |
| Concentration (molar) | 0.5 | 0.25 | 0.5 | 1.0 | 0.5 | 0.5 |
| Approved dose (mmol/kg) | <ul style="list-style-type: none"> Adults and children ≥2 years of age: 0.1 Children <2 years of age: 0.05-0.1 (CNS imaging only) | Adults and children: 0.025 | <ul style="list-style-type: none"> Adults: 0.1 + 2nd dose of 0.2 up to 30 min after 1st dose if needed Children: 0.1 | Adults and children: 0.1 | Adults and children: 0.1 | Adults and children ≥2 years of age: 0.05 |

*Generic version of Dotarem developed by GE Healthcare and branded as Clariscan.
[†]Co-developed by Bracco Diagnostics and Guerbet and marketed under different trade names (Vueway [Bracco Diagnostics] and Elucirem [Guerbet]).
 CNS=central nervous system.

Figure 1. Shoulder MRI in a 17-year-old with palpable back lesion. A 0.05 mmol/kg dose of gadopiclenol at 3T. Initial scan (A) shows enhancing lesion (white arrow) but fat-suppression failure and inadvertent water saturation (red arrows). Repeat scan (B) using two-point Dixon technique shows good enhancement of a desmoid tumor and good signal-to-noise ratio, but with robust fat suppression.



40 million MRI examinations performed annually in the US and in 40% of all pediatric MRI studies.^{1,4}

The six GBCAs currently available for use in children differ in their physicochemical properties, such as structure, stability, relaxivity, ionicity, and viscosity, all of which contribute to their clinical utility and risk profiles (Table 1).⁵⁻¹⁴ When used at therapeutic doses, these agents are generally considered safe; however,

caution should be exercised when imaging certain patient groups.¹⁵

The first disease to be linked to GBCA utilization was nephrogenic systemic fibrosis (NSF), a rare, debilitating, scleroderma-like condition that often progresses to joint contractures and decreased mobility.^{15,16} Nephrogenic systemic fibrosis was first reported in 2000 in a publication that described patients on renal dialysis with scleromyxoedema

symptoms; however, the condition's link to GBCAs was not established until 2006.^{16,17} While the exact mechanism remains unclear, acute or chronic renal impairment is widely believed to increase the risk of NSF in patients exposed to GBCAs.¹⁸ Furthermore, it is believed that the prolonged GBCA clearance time in renally impaired patients increases the opportunity for gadolinium ions to dissociate from the chelate and bind with other anions to create insoluble precipitates that deposit in various tissues.¹⁵

Increased awareness and the regulatory actions implemented since the first report of NSF have led to limited use of GBCAs in at-risk patients, effectively eliminating the occurrence of new cases.¹⁵ In fact, a recent systematic review reported that only seven GBCA-associated NSF cases have occurred since 2008.¹⁹ Additionally, the vast majority of the 639 biopsy-confirmed cases are among adult patients, suggesting that NSF is less common among children.¹⁹ This was confirmed in a 2014 review that identified only 23 pediatric NSF cases reported through September 2012,

Figure 2. A 14-year-old with arthritis and anosmia. A 0.1 mmol/kg dose of gadopicleenol split in two 0.05 mmol/kg doses for imaging of the bilateral hands (A) that shows tenosynovitis (arrows) and normal temporomandibular joints (B, arrows).

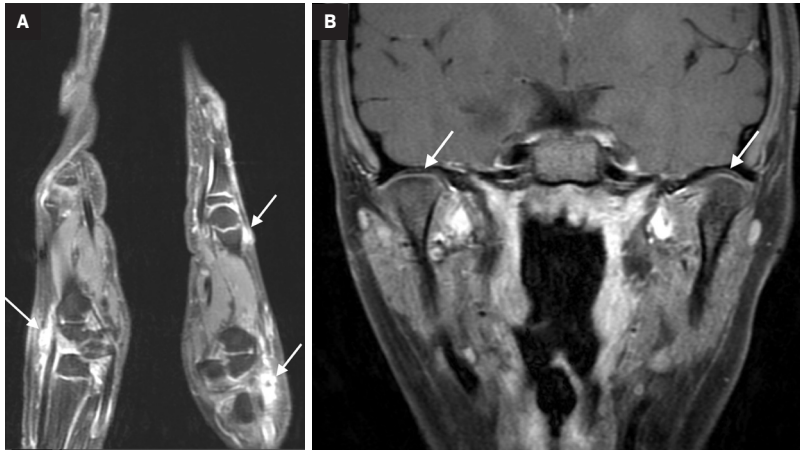


Figure 3. Split of a 0.05 mmol/kg dose of gadopicleenol in two in a 12-year-old with tuberous sclerosis and laser ablation of brain lesions. Brain image (A) shows residual frontal lobe tumors bilaterally (arrows). Reduced-dose imaging of kidneys still has adequate quality for dynamic contrast-enhanced (B) and delayed-phase imaging (C).

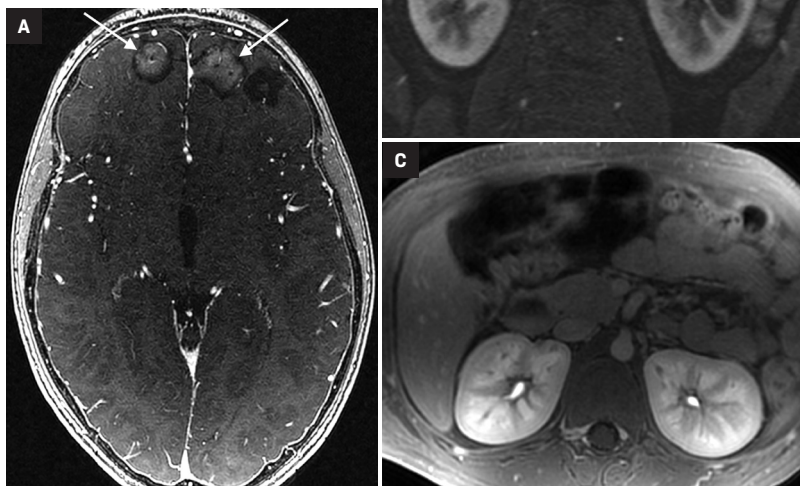
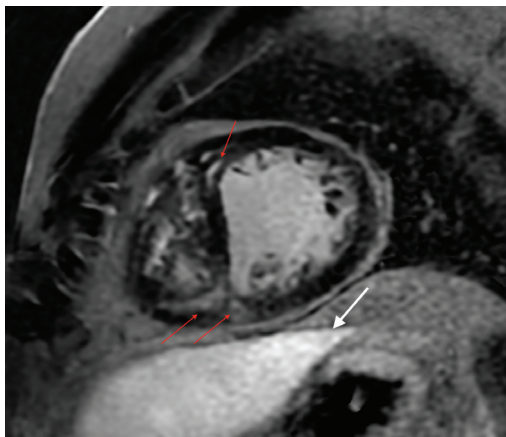


Figure 4. Delayed myocardial enhancement after gadoxetate disodium in a 16-year-old with Fontan-associated liver disease. A 0.05 mmol/kg dose of gadopicleenol at 3T after a single dose of gadoxetate disodium enhances the liver in the hepatobiliary phase (white arrow) and shows regions of abnormal myocardial delayed enhancement (red arrows). The total amount of gadolinium administered is less than what would be administered with most standard extracellular contrast agents.



none of which occurred in patients younger than six years of age.²⁰

GBCA safety has garnered renewed interest in recent years. A 2013 report demonstrated that multiple exposures to GBCA in some patients led to increased signal intensity in specific regions of the brain on unenhanced MR images.²¹ This finding was attributed to the retention of gadolinium compounds in these regions. Since that report, many articles have been published on the topic, with some studies quantifying the levels of gadolinium in different areas of the brains of patients exposed to GBCAs.²²⁻²⁴ These studies confirmed that gadolinium retention occurs to some extent with all GBCAs, regardless of structure or the number of doses administered.²²⁻²⁴ Moreover, gadolinium retention occurs in patients of all ages, with similar distribution and levels in pediatric and adult patients.²⁵

It is important to emphasize that, to date, no reports suggest an association of gadolinium retention with neurotoxicity, even among GBCAs with the highest rates of retention.¹⁵ Although the clinical implications of gadolinium retention remain unknown, that GBCAs provide crucial, even lifesaving, information is well established.¹⁵

Selecting a GBCA for Pediatric MRI

Carefully weighing the benefits of a contrast-enhanced MRI study versus its risks is vitally important in younger patients, as they may undergo repeat exams over their lifetime. As a general principle, the unnecessary exposure of children to GBCAs should be avoided; when a GBCA is necessary, the lowest dose to achieve a diagnosis should be administered.¹⁵ While GBCA selection is guided by its indications and ability to reveal specific structures and pathologies, two key factors, structure and relaxivity, should be considered, as they can influence efficacy and patient safety.

Figure 5. Comprehensive function, flow, anatomy, and tissue characterization in an 11-year-old with repaired tetralogy. A 0.1 mmol/kg dose of gadopicles demonstrated good 4D flow (A) and myocardial delayed enhancement (B).

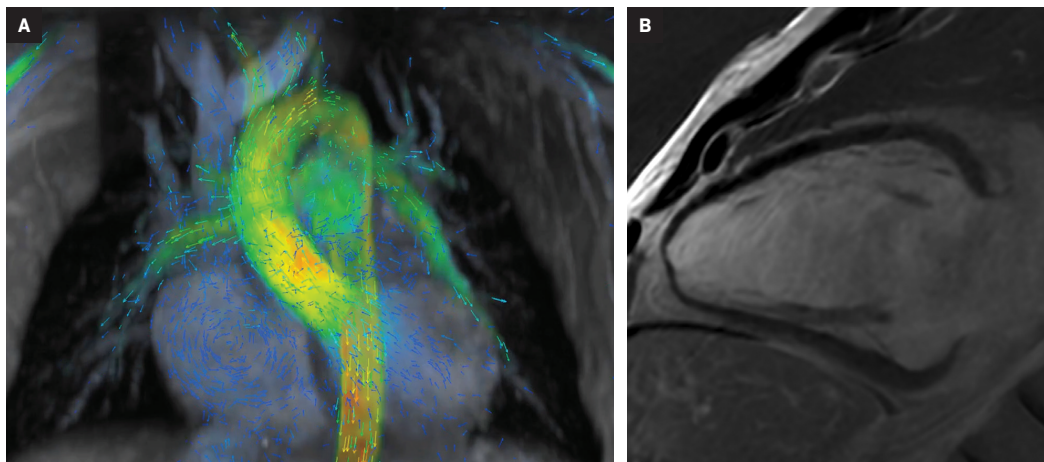
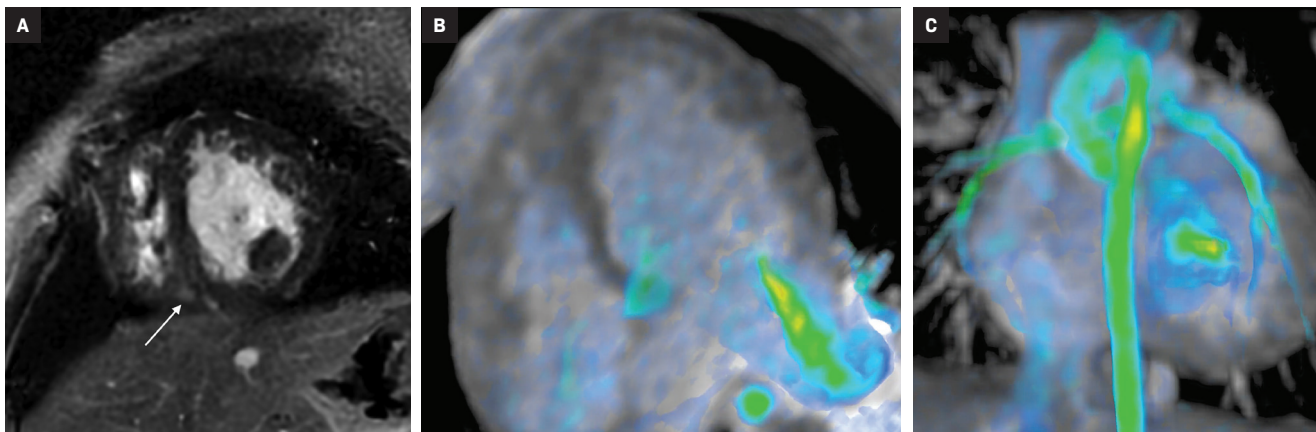


Figure 6. Comprehensive function, flow, anatomy, and tissue characterization with 0.1 mmol/kg dosing of gadopicles in a 2-week-old infant with polyvalvular regurgitation. Despite high heart rate and small patient size, septal delayed enhancement was noted (A, arrow), along with jets of regurgitation through tricuspid and mitral valves (B). Good quality MRA was also obtained (C).



Structure

GBCAs contain the paramagnetic ion gadolinium (Gd^{3+}) bound to a ligand to form a chelate, the structure and ionicity of which influence the overall stability of the chelate- Gd^{3+} complex.¹⁵ Linear nonionic agents demonstrate the lowest stability, whereas linear ionic agents are moderately stable.²⁶ Macrocyclic GBCAs have the highest stability, imparted by a cage-like configuration that allows the chelate to bind Gd^{3+} more tightly than in linear chelates.²⁶ Macrocyclic agents can be postulated to have a lower potential for gadolinium dissociation from the chelate structure, reducing the risk of NSF development or gadolinium retention.²⁷⁻³² While human data are limited, animal studies have shown that gadopicles behaves similarly to

other macrocyclic agents, with less gadolinium retention in tissues compared to linear GBCAs.^{33,34}

With the totality of data supporting the high stability of macrocyclic GBCAs, the shift towards their use in pediatric settings is unsurprising. According to a 2017 survey of children's hospitals in the US, 80% of respondents reported using macrocyclic GBCAs, with 58% reporting having switched in the prior year. An additional 19% said they were considering a switch to a macrocyclic agent.³⁵

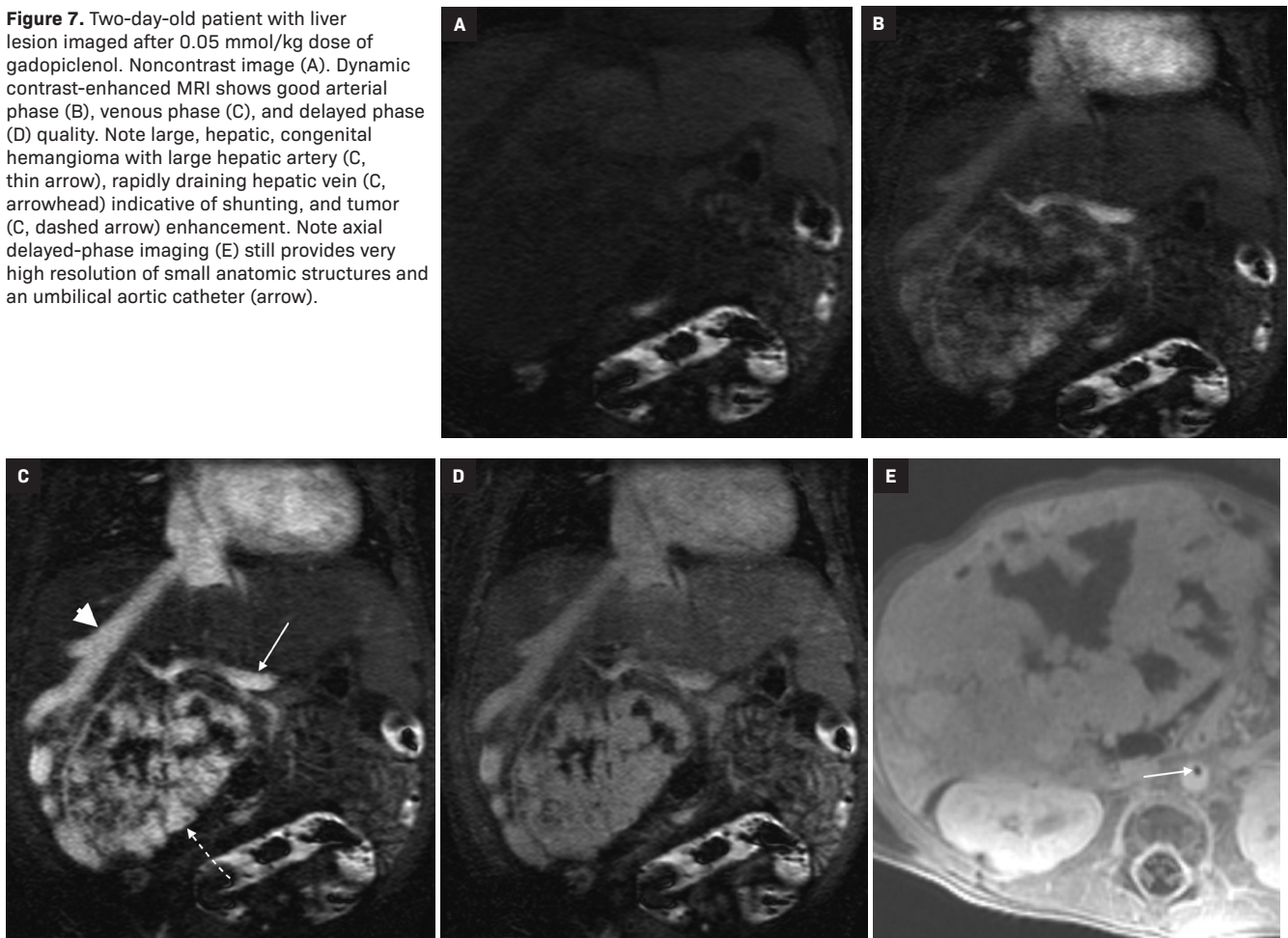
Relaxivity

The ability of GBCAs to increase the relaxation rates of the surrounding water proton spins is quantified in terms of $r1$ relaxivity.³⁶ An agent with a higher $r1$ relaxivity creates better

contrast between abnormal lesions and background tissues, which can help guide diagnosis and treatment planning.³⁶

Of the six available GBCA molecules, three agents—gadoteridol (ProHance), gadoterate meglumine (Dotarem/Clariscan), and gadobutrol (Gadavist)—demonstrate what may be referred to as standard relaxivity values.⁵ The remaining three agents all possess unique properties that contribute to higher relaxivity values. Gadobenate dimeglumine (MultiHance) has a hydrophobic side chain that allows it to transiently interact with serum albumin, slowing the tumbling rate, allowing the Gd^{3+} ion to influence more of the surrounding water protons, and translating into a higher relaxivity.³⁶ The second-highest relaxivity agent,

Figure 7. Two-day-old patient with liver lesion imaged after 0.05 mmol/kg dose of gadopixelenol. Noncontrast image (A). Dynamic contrast-enhanced MRI shows good arterial phase (B), venous phase (C), and delayed phase (D) quality. Note large, hepatic, congenital hemangioma with large hepatic artery (C, thin arrow), rapidly draining hepatic vein (C, arrowhead) indicative of shunting, and tumor (C, dashed arrow) enhancement. Note axial delayed-phase imaging (E) still provides very high resolution of small anatomic structures and an umbilical aortic catheter (arrow).



gadoxetate disodium (Eovist), is selectively taken up by hepatocytes for better visualization of liver tissue.⁸ Gadopixelenol (Vueway/Elucirem) is a macrocyclic agent designed to improve Gd^{3+} ion access to water molecules, resulting in the highest relaxivity of all GBAs, even at high magnetic field strengths.⁶ In clinical studies, a 0.05 mmol/kg dose of gadopixelenol has demonstrated improved diagnostic performance versus conventional GBAs administered at a standard 0.1 mmol/kg dose while maintaining an acceptable safety profile.³⁷⁻³⁹

In the first phase 3 study, PICTURE, 0.05 mmol/kg of gadopixelenol demonstrated noninferiority to 0.1 mmol/kg of gadobutrol for all evaluated parameters for imaging central nervous system (CNS) lesions.³⁸ The percentage of enhancement and lesion-to-background

ratio were significantly higher for gadopixelenol across all blinded readers, and the contrast-to-noise ratio was significantly higher for two of the three readers. Gadopixelenol-enhanced images were preferred by all readers for nearly half of the evaluations.³⁸ In the second phase 3 study, PROMISE, which enrolled 273 adults with at least one suspected focal lesion in one of three different body regions (head and neck; breast, thorax, abdomen, or pelvis; or musculoskeletal system), 0.05 mmol/kg of gadopixelenol was comparable to 0.1 mmol/kg gadobutrol for lesion evaluation.³⁹ Despite being administered at half the gadolinium dose of gadobutrol, gadopixelenol provided a comparable degree of contrast enhancement and quality of morphologic characteristics of lesions.³⁹

Pediatric MRI Experience

There are often multiple challenges to obtaining reliable, high-quality images in pediatric imaging. For instance, our practice at Stanford encounters patients of varying weight, ranging from less than two kilograms to more than 100 kilograms. Establishing an MR protocol that optimally delineates anatomy across that range with reliable signal-to-noise ratio (SNR) can be challenging. Using a high-relaxivity agent like gadopixelenol can enable more robust protocols to reliably achieve a higher SNR for better quality images.

Similarly, for various reasons, repeated image acquisition may be required. For instance, children may fidget, resulting in motion artifacts that may necessitate repeat imaging.

Figure 8. Dynamic contrast-enhanced MRI in a 4-month-old female with liver failure and concern for biliary atresia. Noncontrast image (A), followed by arterial phase depicting hepatic artery (B, arrow), venous phase showing superior mesenteric artery (C, dashed arrow) and portal vein (arrow), and delayed phase showing hepatic vein (D, arrow). Axial delayed image (E) shows that signal-to-noise ratio is maintained despite high spatial resolution.

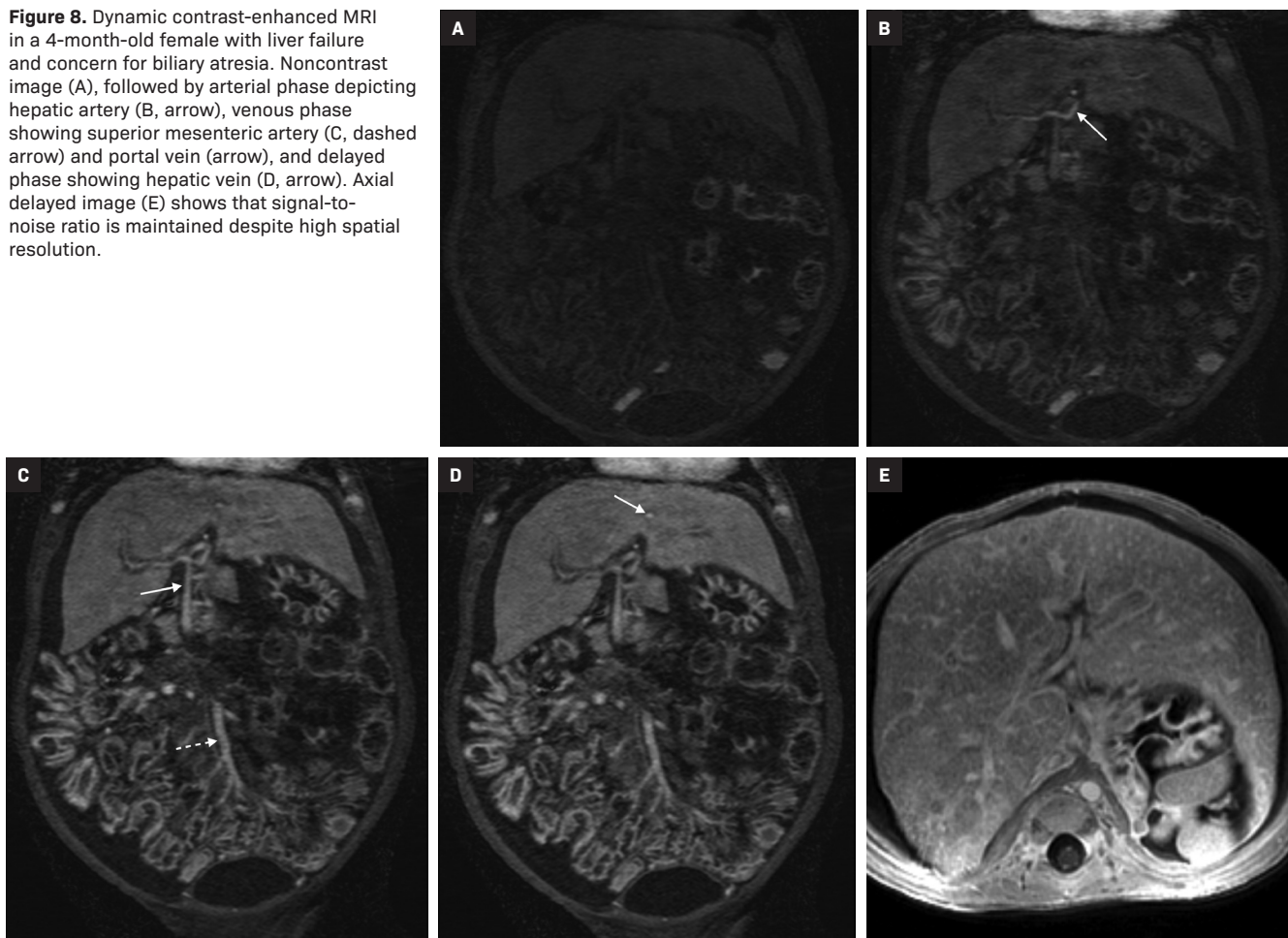
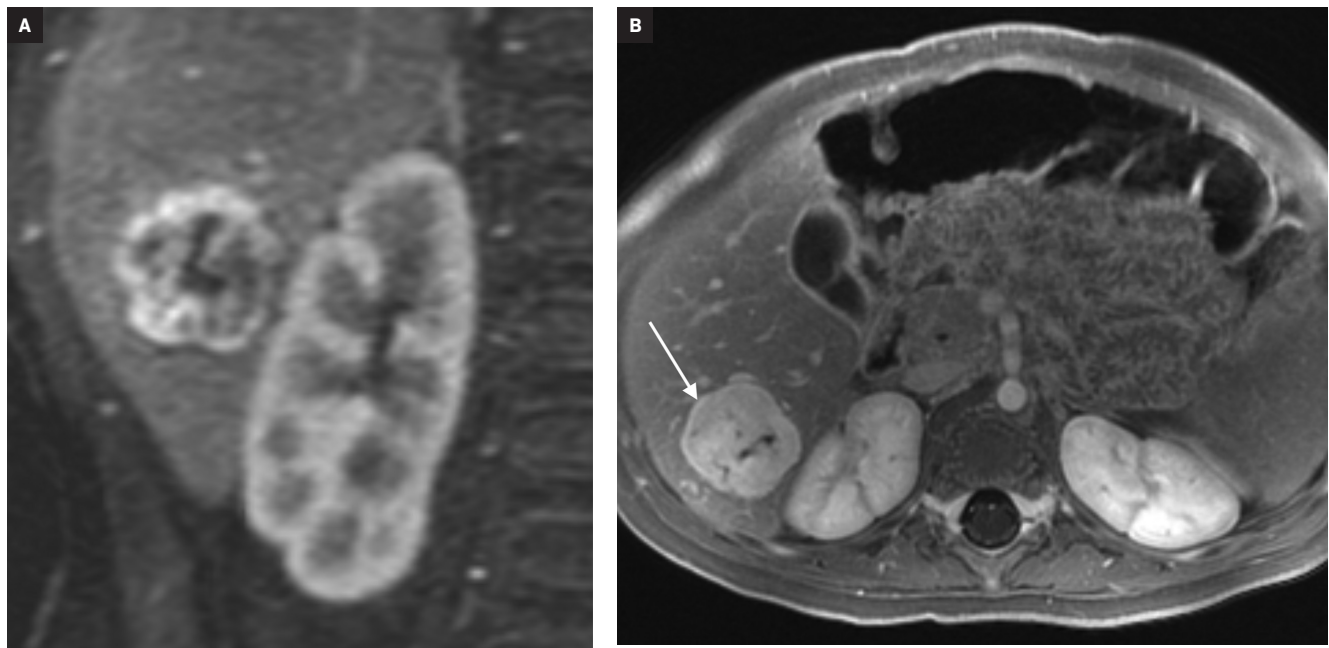


Figure 9. Dynamic contrast-enhanced MRI (A) and high spatial-resolution delayed imaging of a hemangioma (B, arrow) in a 3-month-old infant with 0.05 mmol/kg dosing of gadopicholol.



Summary Points

The development of new GBCAs continues to advance the diagnostic value of MRI. Given that children may undergo repeat exams over their lifetime, weighing the benefits of contrast with its associated risks is crucial. Below is summary of key considerations for GBCA use in children:

- The unnecessary exposure of children to GBCAs should be avoided; when a GBCA is necessary, the lowest dose to achieve a diagnosis should be administered.
- Two physicochemical properties should be considered when selecting a GBCA:
 - Stability: Macrocyclic agents demonstrate the highest stability, with a lower propensity for de-chelation and subsequent risk of NSF development or gadolinium retention.
 - Relaxivity: A high relaxivity agent demonstrates better diagnostic performance and ability to guide diagnosis and treatment planning than a standard relaxivity agent.
- Gadopiclenol is a new, high-relaxivity GBCA with high diagnostic accuracy and efficacy at a lower dose of 0.05 mmol/kg compared with other conventional GBCAs, thus minimizing safety risks without sacrificing diagnostic outcomes.

Moreover, imaging over extremity lengths or other regions with complex air-tissue interfaces may require a second attempt to obtain optimal fat suppression. The higher relaxivity of gadopiclenol may facilitate repeat acquisition without requiring additional contrast dosing (**Figure 1**).

A significant fraction of pediatric MR exams entails evaluation of multiple body parts. In these cases, administering a 0.1 mmol/kg dose of gadopiclenol—which delivers the same number of gadolinium atoms as standard dosing of most other GBCAs—in two 0.05 mmol/kg increments can enable high-quality imaging across the multiple body parts (**Figure 2**). This can be pushed further by splitting a 0.05 mmol/kg dose to maintain high-quality imaging of two body parts (**Figure 3**). As an alternative example, an evaluation of the liver with gadoxetate disodium and an evaluation of myocardial scarring with gadopiclenol can be combined in a single appointment

(**Figure 4**). This is particularly helpful in patients undergoing MRI under anesthesia, as dividing the exam across multiple days would be impractical.

Another challenging pediatric scenario consists of a comprehensive cardiac MRI assessment of anatomy, blood flow, ventricular function, and myocardial tissue characterization. Here a 0.1 mmol/kg dose of gadopiclenol enables a complete exam within ten minutes in a preteen child (**Figure 5**) or an infant (**Figure 6**). In the case of an uncooperative child, that can mean the difference between obtaining a study with sufficient image quality and one without.

A shorter scan with the ability to capture rapid kinetics in children is especially useful in abdominal imaging. Similarly, in angiography exams, the high relaxivity of gadopiclenol can capture the first pass at high spatiotemporal resolution, thus facilitating higher matrix size and thinner slices for improved arterial delineation (**Figures 7–9**).

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