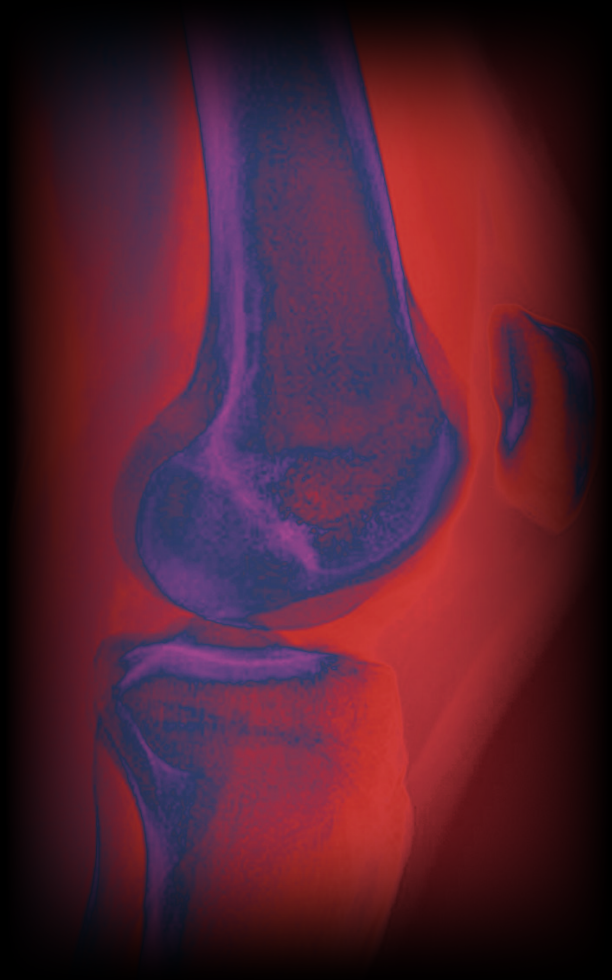
January / February 2023
Volume 52, Number 1

Applied Radiology

AppliedRadiology®

YEARS

The Journal of Practical Medical Imaging and Management



SA–CME
Worrisome and Incidental Signs on Knee Radiographs in Clinical Practice: Traumatic and Degenerative Lesions

Giant Sigmoid Diverticulum: Imaging Features and Management

Mentoring for Success in Academic Radiology

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Surfactant Protein C Deficiency-associated Diffuse Lung Disease

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The individual who appears is for illustrative purposes. The person depicted is a model and not a real healthcare professional.
Please see Brief Summary of Prescribing Information including Boxed Warning on adjacent page.

VUEWAY™ (gadopiclenol) solution for injection

Indications
VUEWAY injection is indicated in adults and children aged 2 years and older for use with magnetic resonance imaging (MRI) to detect and visualize lesions with abnormal vascularity in:

- the central nervous system (brain, spine and surrounding tissues),
- the body (head and neck, thorax, abdomen, pelvis, and musculoskeletal system).

IMPORTANT SAFETY INFORMATION

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.

- **The risk for NSF appears highest among patients with:**
  - **Chronic, severe kidney disease (GFR <30 mL/min/1.73 m^2), or**
  - **Acute kidney injury.**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age >60 years, hypertension, diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.**
- **For patients at highest risk for NSF, do not exceed the recommended VUEWAY dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration.**

Contraindications
VUEWAY injection is contraindicated in patients with history of hypersensitivity reactions to VUEWAY.

Warnings
Risk of **nephrogenic systemic fibrosis** is increased in patients using GBCA agents that have impaired elimination of the drugs, with the highest risk in patients chronic, severe kidney disease as well as patients with acute kidney injury. Avoid use of GBCAs among these patients unless the diagnostic information is essential and not available with non-contrast MRI or other modalities.

Hypersensitivity reactions, including serious hypersensitivity reactions, could occur during use or shortly following VUEWAY administration. Assess all patients for any history of a reaction to contrast media, bronchial asthma and/or allergic disorders, administer VUEWAY only in situations where trained personnel and therapies are promptly available for the treatment of hypersensitivity reactions, and observe patients for signs and symptoms of hypersensitivity reactions after administration.

INTRODUCING

Vueway™
(gadopiclenol) injection
485.1 mg/mL

HALF THE GADOLINIUM DOSE COMPARED TO OTHER MACROCYCLIC GBCAS IN APPROVED INDICATIONS.[1,3-6] FROM BRACCO, YOUR TRUSTED PARTNER IN MRI.

BRACCO
LIFE FROM INSIDE

Gadolinium retention can be for months or years in several organs after administration. The highest concentrations (nanomoles per gram of tissue) have been identified in the bone, followed by other organs (brain, skin, kidney, liver and spleen). Minimize repetitive GBCA imaging studies, particularly closely spaced studies, when possible.

Acute kidney injury requiring dialysis has occurred with the use of GBCAs in patients with chronically reduced renal function. The risk of acute kidney injury may increase with increasing dose of the contrast agent.

Ensure catheter and venous patency before injecting as **extravasation** may occur, and cause tissue irritation.

VUEWAY may **impair the visualization of lesions** seen on non-contrast MRI. Therefore, caution should be exercised when Vueway MRI scans are interpreted without a companion non-contrast MRI scan.

The most common adverse reactions (incidence ≥ 0.5%) are injection site pain (0.7%), and headache (0.7%).

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see BRIEF SUMMARY of Prescribing Information for VUEWAY, including BOXED WARNING on Nephrogenic Systemic Fibrosis.

Manufactured for Bracco Diagnostics Inc. by Liebel-Flarsheim Company LLC - Raleigh, NC, USA 27616.

VUEWAY is a trademark of Bracco Imaging S.p.A.

References: 1. Vueway™ (gadopiclenol) Injection Full Prescribing Information. Monroe Twp., NJ: Bracco Diagnostics Inc.; September 2022. **2.** Robic C, Port M, Rousseaux O, et al. Physicochemical and Pharmacokinetic Profiles of Gadopiclenol: A New Macrocyclic Gadolinium Chelate With High T1 Relaxivity. *Invest Radiol.* 2019 Aug;54: 475–484. **3.** GADAVIST® (gadobutrol) Injection. Full Prescribing Information. Bayer HealthCare Pharmaceuticals Inc. Whippany, NJ; April 2022. **4.** DOTAREM® (gadoterate meglumine) Injection. Full Prescribing Information. Guerbet LLC. Princeton, NJ; April 2022. **5.** CLARISCAN™ (gadoterate meglumine) injection for intravenous use. Full Prescribing Information. GE Healthcare. Marlborough, MA; February 2020. **6.** ProHance® (Gadoteridol) Injection. Full Prescribing Information and Patient Medication Guide. Monroe Twp., NJ: Bracco Diagnostics Inc.; December 2020.

VISIT VUEWAY.COM FOR MORE INFORMATION

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Toll Free: 1-877-272-2269 (U.S. only)
Fax: 609-514-2446

BRACCO **Bracco Diagnostics**

multihance®
(gadobenate dimeglumine)
injection, 529 mg/mL

Rx ONLY
Please see full prescribing information.
A brief summary follows.

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs.

Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrast MRI or other modalities. NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle and internal organs.

- The risk for NSF appears highest among patients with:
  - chronic, severe kidney disease (GFR <30 mL/min/1.73m2), or
  - acute kidney injury.
- Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.
- For patients at highest risk for NSF, do not exceed the recommended MultiHance dose and allow a sufficient period of time for elimination of the drug from the body prior to re-administration. [see ***Warnings and Precautions (5.1)***]

1 INDICATIONS AND USAGE

1.1 MRI of the Central Nervous System (CNS)

MultiHance is indicated for intravenous use in magnetic resonance imaging (MRI) of the central nervous system (CNS) in adults and pediatric patients (including term neonates), to visualize lesions with abnormal blood-brain barrier or abnormal vascularity of the brain, spine, and associated tissues.

1.2 MRA of Renal and Aorto-ilio-femoral Vessels

MultiHance is indicated for use in magnetic resonance angiography (MRA) to evaluate adults with known or suspected renal or aorto-ilio-femoral occlusive vascular disease.

4 CONTRAINDICATIONS MultiHance is contraindicated in patients with known allergic or hypersensitivity reactions to gadolinium-based contrast agents [see ***Warnings and Precautions (5.2)***].

5 WARNINGS AND PRECAUTIONS

5.1 Nephrogenic Systemic Fibrosis (NSF) Gadolinium-based contrast agents (GBCAs) increase the risk for nephrogenic systemic fibrosis (NSF) among patients with impaired elimination of the drugs. Avoid use of GBCAs among these patients unless the diagnostic information is essential and not available with non-contrast enhanced MRI or other modalities. The GBCA-associated NSF risk appears highest for patients with chronic, severe kidney disease (GFR <30 mL/min/1.73m^2) as well as patients with acute kidney injury. The risk appears lower for patients with chronic, moderate kidney disease (GFR 30-59 mL/min/1.73m^2) and little, if any, for patients with chronic, mild kidney disease (GFR 60-89 mL/min/1.73m^2). NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs. Report any diagnosis of NSF following MultiHance administration to Bracco Diagnostics (1-800-257-5181) or FDA (1-800-FDA-1088 or www.fda.gov/medwatch).

Screen patients for acute kidney injury and other conditions that may reduce renal function.

Features of acute kidney injury consist of rapid (over hours to days) and usually reversible decrease in kidney function, commonly in the setting of surgery, severe infection, injury or drug-induced kidney toxicity. Serum creatinine levels and estimated GFR may not reliably assess renal function in the setting of acute kidney injury. For patients at risk for chronically reduced renal function (e.g., age > 60 years, diabetes mellitus or chronic hypertension), estimate the GFR through laboratory testing.

Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA and the degree of renal impairment at the time of exposure. Record the specific GBCA and the dose administered to a patient. For patients at highest risk for NSF, do not exceed the recommended MultiHance dose and allow a sufficient period of time for elimination of the drug prior to re-administration. For patients receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of a GBCA in order to enhance the contrast agent's elimination. The usefulness of hemodialysis in the prevention of NSF is unknown [see ***Dosage and Administration (2) and Clinical Pharmacology (12)***].

5.2 Hypersensitivity Reactions Anaphylactic and anaphylactoid reactions have been reported, involving cardiovascular, respiratory, and/or cutaneous manifestations. Some patients experienced circulatory collapse and died. In most cases, initial symptoms occurred within minutes of MultiHance administration and resolved with prompt emergency treatment. Prior to MultiHance administration, ensure the availability of personnel trained and medications to treat hypersensitivity reactions. If such a reaction occurs stop MultiHance and immediately begin appropriate therapy. Additionally, consider the risk for hypersensitivity reactions, especially in patients with a history of hypersensitivity reactions or a history of asthma or other allergic disorders. Observe patients for signs and symptoms of a hypersensitivity reaction during and for up to 2 hours after MultiHance administration.

5.3 Gadolinium Retention Gadolinium is retained for months or years in several organs. The highest concentrations (nanomoles per gram of tissue) have been identified in the bone, followed by other organs (e.g. brain, skin, kidney, liver, and spleen. The duration of retention also varies by tissue and is longest in bone. Linear GBCAs cause more retention than macrocyclic GBCAs. At equivalent doses, gadolinium retention varies among the linear agents with Omniscan (gadodiamide) and Optimark (gadoversetamide) causing greater retention than other linear agents [Eovist (gadoxetate disodium), Magnevist (gadopentetate dimeglumine), MultiHance (gadobenate dimeglumine)]. Retention is lowest and similar among the macrocyclic GBCAs [Dotarem gadoterate meglumine), Gadavist (gadobutrol), ProHance (gadoteridol)].

Consequences of gadolinium retention in the brain have not been established. Pathologic and clinical consequences of GBCA administration and retention in skin and other organs have been established in patients with impaired renal function [see ***Warnings and Precautions (5.1)***]. There are rare reports of pathologic skin changes in patients with normal renal function. Adverse events involving multiple organ systems have been reported in patients with normal renal function without an established causal link to gadolinium retention [see ***Adverse Reactions (6.2)***]. While clinical consequences of gadolinium retention have not been established in patients with normal renal function, certain patients might be at higher risk. These include patients requiring multiple lifetime doses, pregnant and pediatric patients, and patients with inflammatoryconditions. Consider the retention characteristics of the agent when choosing a GBCA for these patients. Minimize repetitive GBCA imaging studies, particularly closely spaced studies when possible.

5.4 Acute Renal Failure In patients with renal insufficiency, acute renal failure requiring dialysis or worsening renal function have occurred with the use of gadolinium-based contrast agents. The risk of renal failure may increase with increasing dose of the contrast agent. Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. Consider follow-up renal function assessments for patients with a history of renal dysfunction.

5.5 Extravasation and Injection Site Reactions Extravasation of MultiHance may lead to injection site reactions, characterized by local pain or burning sensation, swelling, blistering, and necrosis. In animal experiments, local reactions including eschar and necrosis were noted even on Day 8 post perivenous injection of MultiHance. Exercise caution to avoid local extravasation during intravenous administration of MultiHance. If extravasation occurs, evaluate and treat as necessary if local reactions develop.

5.6 Cardiac Arrhythmias Cardiac arrhythmias have been observed in patients receiving MultiHance in clinical trials [see ***Adverse Reactions (6.1)***]. Assess patients for underlying conditions or medications that predispose to arrhythmias.

A double-blind, placebo-controlled, 24-hour post dose continuous monitoring, crossover study in 47 subjects evaluated the effect of 0.2 mmol/kg MultiHance on ECG intervals including QTc. The average changes in QTc values compared with placebo were minimal (<5 msec). QTc prolongation between 30 and 60 msec were noted in 20 subjects who received MultiHance vs. 11 subjects who received placebo. Prolongations ≥ 61 msec were noted in 6 subjects who received MultiHance and in 3 subjects who received placebo. None of these subjects had associated malignant arrhythmias. The effects on QTc by MultiHance dose, other drugs, and medical conditions were not systematically studied.

5.7 Interference with Visualization of Certain Lesions Certain lesions seen on non-contrast images may not be seen on contrast-images. Exercise caution when interpreting contrast MR images in the absence of companion non-contrast MR images.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:
- Nephrogenic systemic fibrosis [see ***Warnings and Precautions (5.1)***]
- Hypersensitivity reactions [see ***Warnings and Precautions (5.2)***]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adult In clinical trials with MultiHance, a total of 4967 adult subjects (137 healthy volunteers and 4830 patients) received MultiHance at doses ranging from 0.005 to 0.4 mmol/kg. There were 2938 (57%) men and 2129 (43%) women with a mean age of 56.5 years (range 18 to 93 years). A total of 4403 (89%) subjects were Caucasian, 134 (3%) Black, 275 (6%) Asian, 40 (1%) Hispanic, 70 (1%) in other racial groups, and for 45 (1%) subjects, race was not reported.

The most commonly reported adverse reactions in adult subjects who received MultiHance were nausea (1.3%) and headache (1.2%). Most adverse reactions were mild to moderate in intensity. One subject experienced a serious anaphylactoid reaction with laryngeal spasm and dyspnea [see ***Warnings and Precautions (5.2)***]. Serious adverse reactions consisting of convulsions, pulmonary edema, acute necrotizing pancreatitis, and anaphylactoid reactions were reported in 0.1% of subjects in clinical trials.

Adverse reactions that occurred in at least 0.5% of 4967 adult subjects who received MultiHance are listed below (Table 2), in decreasing order of occurrence within each system.

TABLE 2: ADVERSE REACTIONS REPORTED IN ≥ 0.5% OF ADULT SUBJECTS WHO RECEIVED MULTIHANCE IN CLINICAL TRIALS

Number of subjects dosed	4967
Number of subjects with any adverse reaction	517 (10.4%)
Gastrointestinal Disorders	
Nausea	67 (1.3%)
General Disorders and Administration Site Disorders	
Injection Site Reaction	54 (1.1%)
Feeling Hot	49 (1.0%)
Nervous System Disorders	
Headache	60 (1.2%)
Dysgeusia	33 (0.7%)
Paresthesia	24 (0.5%)
Dizziness	24 (0.5%)

The following adverse reactions occurred in less than 0.5% of the 4967 adult subjects who received MultiHance. Serious adverse reactions described above are not repeated below.

Blood and Lymphatic System Disorders: Basophilia; **Cardiac Disorders:** Atrioventricular block first degree; **Eye Disorders:** Eye pruritus, eye swelling, ocular hyperemia, visual disturbance; **Gastrointestinal Disorders:** Abdominal pain or discomfort, diarrhea, dry mouth, lip swelling, paraesthesia oral, tongue edema, vomiting; **General Disorders and Administration Site Conditions:** Chest pain or discomfort, chills, malaise; **Immune System Disorders:** Hypersensitivity; **Investigations:** Nonspecific changes in laboratory tests (including hematology, blood chemistry, liver enzymes and urinalysis), blood pressure and electrocardiogram parameters (including PR, QRS and QT intervals and ST-T segment changes). **Musculoskeletal and Connective Tissue Disorders:** Myalgia; **Nervous System Disorders:** Parosmia, tremor; **Respiratory, Thoracic and Mediastinal Disorders:** Dyspnea, laryngospasm, nasal congestion, sneezing, wheezing; **Skin and Subcutaneous Tissue Disorders:** Hyperhidrosis, pruritus, rash, swelling face, urticaria.

Pediatric In clinical trials of MultiHance in MRI of the CNS, 217 pediatric subjects received MultiHance at a dose of 0.1 mmol/kg. A total of 112 (52%) subjects were male and the overall mean age was 8.3 years (range 4 days to 17 years). A total of 168 (77%) subjects were Caucasian, 12 (6%) Black, 12 (6%) Asian, 24 (11%), Hispanic, and 1 (<1%) in other racial groups.

Adverse reactions were reported for 14 (6.5%) of the subjects. The frequency and the nature of the adverse reactions were similar to those seen in the adult patients. The most commonly reported adverse reactions were vomiting (1.4%), pyrexia (0.9%), and hyperhidrosis (0.9%). No subject died during study participation. A serious adverse reaction of worsening of vomiting was reported for one (0.5%) patient with a brain tumor (glioma) for which a causal relationship to MultiHance could not be excluded.

Pediatric Patients In clinical trials of MultiHance in MRI of the CNS, 307 pediatric subjects received MultiHance at a dose of 0.1 mmol/kg. A total of 160 (52%) subjects were male and the overall mean age was 6.0 years (range, 2 days to 17 years). A total of 211 (69%) subjects were Caucasian, 24 (8%) Black, 15 (5%) Asian, 39 (13%), Hispanic, 2 (<1%) in other racial groups, and for 16 (5%), race was not reported. Adverse reactions were reported for 14 (4.6%) of the subjects. The frequency and the nature of the adverse reactions were similar to those seen in the adult patients. The most commonly reported adverse reactions were vomiting (1.0%), pyrexia (0.7%), and hyperhidrosis (0.7%). No subject died during study participation.

6.2 Post-marketing Experience

The following adverse reactions have been identified during post approval use of MultiHance. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Anaphylactic, anaphylactoid and hypersensitivity reactions manifested with various degrees of severity up to anaphylactic shock, loss of consciousness and death. The reactions generally involved signs or symptoms of respiratory, cardiovascular, and/or mucocutaneous abnormalities.

General Disorders and Administration Site Conditions: Extravasation of MultiHance may lead to injection site reactions, characterized by local pain or burning sensation, swelling, blistering, and necrosis [***see Warnings and Precautions (5.4)***]. Adverse events with variable onset and duration have been reported after GBCA administration [***see Warnings and Precautions (5.3)***]. These include fatigue, asthenia, pain syndromes, and heterogeneous clusters of symptoms in the neurological, cutaneous, and musculoskeletal systems.

Skin: Gadolinium associated plaques.

7 DRUG INTERACTIONS

7.1 Transporter-Based Drug-Drug Interactions MultiHance and other drugs may compete for the canalicular multispecific organic anion transporter (MOAT also referred to as MRP2 or ABCC2). Therefore MultiHance may prolong the systemic exposure of drugs such as cisplatin, anthracyclines (e.g. doxorubicin, daunorubicin), vinca alkaloids (e.g. vincristine), methotrexate, etoposide, tamoxifen, and paclitaxel. In particular, consider the potential for prolonged drug exposure in patients with decreased MOAT activity (e.g. Dubin Johnson syndrome).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Risk Summary GBCAs cross the placenta and result in fetal exposure and gadolinium retention. The human data on the association between GBCAs and adverse fetal outcomes are limited and inconclusive (see Data). In animal reproduction studies, gadobenate dimeglumine has been shown to be teratogenic in rabbits following repeated intravenous administration during organogenesis at doses up to 6 times the recommended human dose. There were no adverse developmental effects observed in rats with intravenous administration of gadobenate dimeglumine during organogenesis at doses up to three times the recommended human dose (see Data). Because of the potential risks of gadolinium to the fetus, use MultiHance only if imaging is essential during pregnancy and cannot be delayed. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and is 15 to 20%, respectively.

Data *Human Data* Contrast enhancement is visualized in the human placenta and fetal tissues after maternal GBCA administration. Cohort studies and case reports on exposure to GBCAs during pregnancy have not reported a clear association between GBCAs and adverse effects in the exposed neonates. However, a retrospective cohort study, comparing pregnant women who had a GBCA MRI to pregnant women who did not have an MRI, reported a higher occurrence of stillbirths and neonatal deaths in the group receiving GBCA MRI. Limitations of this study include a lack of comparison with non-contrast MRI and lack of information about the maternal indication for MRI. Overall, these data preclude a reliable evaluation of the potential risk of adverse fetal outcomes with the use of GBCAs in pregnancy. *Animal Data* Gadolinium Retention GBCAs administered to pregnant non-human primates (0.1 mmol/kg on gestational days 85 and 135) result in measurable gadolinium concentration in the offspring in bone, brain, skin, liver, kidney, and spleen for at least 7 months. GBCAs administered to pregnant mice (2 mmol/kg daily on gestational days 16 through 19) result in measurable gadolinium concentrations in the pups in bone, brain, kidney, liver, blood, muscle, and spleen at one month postnatal age.

Reproductive Toxicology Gadobenate dimeglumine has been shown to be teratogenic in rabbits when administered intravenously at 2 mmol/kg/day (6 times the recommended human dose based on bodysurface area) during organogenesis (day 6 to 18) inducing microphthalmia/small eye and/or focal retinal fold in 3 fetuses from 3 separate litters. In addition, MultiHance intravenously administered at 3 mmol/kg/day (10 times the recommended human dose based on body surface area) has been shown to increase intrauterine deaths in rabbits. There was no evidence that MultiHance induced teratogenic effects in rats at doses up to 2 mmol/kg/day (3 times the recommended human dose based on body surface area), however, rat dams exhibited no systemic toxicity at this dose. There were no adverse effects on the birth, survival, growth, development and fertility of the F1 generation at doses up to 2 mmol/kg in a rat peri- and post-natal (Segment III) study.

10 OVERDOSAGE

Clinical consequences of overdosage with MultiHance have not been reported. Treatment of an overdosage should be directed toward support of vital functions and prompt institution of symptomatic therapy. In a Phase 1 clinical study, doses up to 0.4 mmol/kg were administered to patients. MultiHance has been shown to be dialyzable [see ***Clinical Pharmacology (12.3)***].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action Gadobenate dimeglumine is a paramagnetic agent and, as such, develops a magnetic moment when placed in a magnetic field. The large magnetic moment produced by the paramagnetic agent results in a large local magnetic field, which can enhance the relaxation rates of water protons in its vicinity leading to an increase of signal intensity (brightness) of tissue.

In magnetic resonance imaging (MRI), visualization of normal and pathological tissue depends in part on variations in the radiofrequency signal intensity that occur with 1) differences in proton density; 2) differences of the spin-lattice or longitudinal relaxation times (T1); and 3) differences in the spin-spin or transverse relaxation time (T2). When placed in a magnetic field, gadobenate dimeglumine decreases the T1 and T2 relaxation time in target tissues. At recommended doses, the effect is observed with greatest sensitivity in the T1-weighted sequences.

12.2 Pharmacodynamics Unlike other tested paramagnetic contrast agents (See Table 3), MultiHance demonstrates weak and transient interactions with serum proteins that causes slowing in the molecular tumbling dynamics, resulting in strong increases in relaxivity in solutions containing serum proteins. The improved relaxation effect can contribute to increased contrast-to-noise ratio and lesion-to-brain ratio, which may improve visualization.

TABLE 3: RELAXIVITY (mM^{-1}s^{-1}) OF GADOLINIUM CHELATES

	Human plasma	
	r_1	r_2
Gadobenate	9.7[1]	12.5[1]
Gadopentetate	4.9[1]	6.3[1]
Gadodiamide	5.4[2]	---
Gadoteridol	5.4[2]	---

r_1 and r_2 relaxivities indicate the efficiency in shortening T1 and T2 relaxation times, respectively.
[1] In heparinized human plasma, at 39°C.
[2] In citrated human plasma, at 37°C.
--- Not available

Disruption of the blood-brain barrier or abnormal vascularity allows enhancement by MultiHance of lesions such as neoplasms, abscesses, and infarcts. Uptake of MultiHance into hepatocytes has been demonstrated.

12.3 Pharmacokinetics Three single-dose intravenous studies were conducted in 32 healthy male subjects to assess the pharmacokinetics of gadobenate dimeglumine. The doses administered in these studies ranged from 0.005 to 0.4 mmol/kg. Upon injection, the meglumine salt is completely dissociated from the gadobenate dimeglumine complex. Thus, the pharmacokinetics is based on the assay of gadobenate ion, the MRI contrast effective ion in gadobenate dimeglumine. Data for plasma concentration and area under the curve demonstrated linear dependence on the administered dose. The pharmacokinetics of gadobenate ion following intravenous administration can be best described using a two-compartment model.

Distribution Gadobenate ion has a rapid distribution half-life (reported as mean ± SD) of 0.084 ± 0.012 to 0.605 ± 0.072 hours. Volume of distribution of the central compartment ranged from 0.074 ± 0.017 to 0.158 ± 0.038 L/kg, and estimates of volume of distribution by area ranged from 0.170 ± 0.016 to 0.282 ± 0.079 L/kg. These latter estimates are approximately equivalent to the average volume of extracellular body water in man. *In vitro* studies showed no appreciable binding of gadobenate ion to human serum proteins.

Elimination Gadobenate ion is eliminated predominately via the kidneys, with 78% to 96% of an administered dose recovered in the urine. Total plasma clearance and renal clearance estimates of gadobenate ion were similar, ranging from 0.093 ± 0.010 to 0.133 ± 0.270 L/hr/kg and 0.082 ± 0.007 to 0.104 ± 0.039 L/hr/kg, respectively. The clearance is similar to that of substances that are subject to glomerular filtration. The mean elimination half-life ranged from 1.17 ± 0.26 to 2.02 ± 0.60 hours. A small percentage of the administered dose (0.6% to 4%) is eliminated via the biliary route and recovered in feces.

Metabolism There was no detectable biotransformation of gadobenate ion. Dissociation of gadobenate ion *in vivo* has been shown to be minimal, with less than 1% of the free chelating agent being recovered alone in feces.

Pharmacokinetics in Special Populations

Renal Impairment: A single intravenous dose of 0.2 mmol/kg of MultiHance was administered to 20 subjects with impaired renal function (6 men and 3 women with moderate renal impairment [urine creatinine clearance >30 to <60 mL/min] and 5 men and 6 women with severe renal impairment [urine creatinine clearance >10 to <30 mL/min]). Mean estimates of the elimination half-life were 6.1 ± 3.0 and 9.5 ± 3.1 hours for the moderate and severe renal impairment groups, respectively as compared with 1.0 to 2.0 hours in healthy volunteers.

Hemodialysis: A single intravenous dose of 0.2 mmol/kg of MultiHance was administered to 11 subjects (5 males and 6 females) with end-stage renal disease requiring hemodialysis to determine the pharmacokinetics and dialyzability of gadobenate. Approximately 72% of the dose was recovered by hemodialysis over a 4-hour period. The mean elimination half-life on dialysis was 1.21 ± 0.29 hours as compared with 42.4 ± 24.4 hours when off dialysis.

Hepatic Impairment: A single intravenous dose of 0.1 mmol/kg of MultiHance was administered to 11 subjects (8 males and 3 females) with impaired liver function (Class B or C modified Child-Pugh Classification). Hepatic impairment had little effect on the pharmacokinetics of MultiHance with the parameters being similar to those calculated for healthy subjects.

Gender, Age, Race: A multiple regression analysis performed using pooled data from several pharmacokinetic studies found no significant effect of sex upon the pharmacokinetics of gadobenate. Clearance appeared to decrease slightly with increasing age. Since variations due to age appeared marginal, dosage adjustment for geriatric population is not recommended. Pharmacokinetic differences due to race have not been systematically studied.

Pediatric: A population pharmacokinetic analysis incorporated data from 25 healthy subjects (14 males and 11 females) and 15 subjects undergoing MR imaging of the central nervous system (7 males and 8 females) betweenages of 2 and 16 years. The subjects received a single intravenous dose of 0.1 mmol/kg of MultiHance. The geometric mean Cmax was 62.3 µg/mL (n=16) in children 2 to 5 years of age, and 64.2 µg/mL (n=24) in children older than 5 years. The geometric mean AUC 0-∞ was 77.9 µg·h/mL in children 2-5 years of age (n=16) and 82.6 µg·h/mL in children older than 5 years (n=24). The geometric mean half-life was 1.2 hours in children 2 to 5 years of age and 0.93 hours in children older than 5 years. There was no significant gender-related difference in the pharmacokinetic parameters in the pediatric patients. Over 80% of the dose was recovered in urine after 24 hours. Pharmacokinetic simulations indicate similar AUC and Cmax values for MultiHance in pediatric subjects less than 2 years when compared to those reported for adults; no age-based dose adjustment is necessary forthis pediatric population.

17 PATIENT COUNSELING INFORMATION

17.1 Nephrogenic Systemic Fibrosis Instruct patients to inform their physician if they:
• have a history of kidney and/or liver disease, or • have recently received a GBCA.

GBCAs increase the risk for NSF among patients with impaired elimination of the drugs. To counsel patients at risk for NSF: • Describe the clinical manifestations of NSF • Describe procedures to screen for the detection of renal impairment.

Instruct the patients to contact their physician if they develop signs or symptoms of NSF following MultiHance administration, such as burning, itching, swelling, scaling, hardening and tightening of the skin; red or dark patches on the skin; stiffness in joints with trouble moving, bending or straightening the arms, hands, legs or feet; pain in the hip bones or ribs; or muscle weakness.

17.2 Common Adverse Reactions

Inform patients that they may experience:
• reactions along the venous injection site, such as mild and transient burning or pain or feeling of warmth or coldness at the injection site • side effects of feeling hot, nausea, and headache.

17.3 General Precautions

Instruct patients scheduled to receive MultiHance to inform their physician if they:
• are pregnant or breast feeding • have a history of renal disease, heart disease, seizure, asthma or allergic respiratory diseases • are taking any medications • have any allergies to any of the ingredients of MultiHance.

Rx only US Patent No. 4,916,246 Manufactured for Bracco Diagnostics Inc. Monroe Township, NJ 08831 By Patheon Italia S.p.A. - 03013 Ferentino (Italy) Revised October 2018 18-061418B

†Multicenter double-blind randomized intraindividual crossover study design of 123 patients with known or suspected brain tumors. Each patient received 0.1-mmol/kg doses of MultiHance and Gadavist in 2 identical MR imaging examinations. Contrast agents were administered by IV using manual bolus injection (n=118) or a power injector (n=4). Both agents were administered at 0.1 mmol/kg of body weight, corresponding to 0.2 mL/kg for MultiHance and 0.1 mL/kg for Gadavist. The interval between the 2 MR imaging examinations was >48 hours to avoid carryover effects but <14 days to minimize the chance of measurable disease progression or lesion evolution. All images were evaluated by 3 blinded, independent experienced radiologists who were unaffiliated with the study centers. Each reader evaluated the patient images separately and independently. Images were evaluated qualitatively for diagnostic information and scored for: 1) lesion border delineation, 2) disease extent, 3) visualization of lesion internal morphology, and 4) lesion contrast enhancement compared with surrounding normal tissue. All assessments used a 3-point scales from 1 (examination 1 superior) through 0 (examinations equal) to 1 (examination 2 superior).

Gadavist® (gadobutrol) is a registered trademark of Bayer Healthcare. **Reference:** Seidl Z, Vymazal J, Mechl M, et al. Does higher gadolinium concentration play a role in the morphologic assessment of brain tumors? Results of a multicenter intraindividual crossover comparison of gadobutrol versus gadobenate dimeglumine (the MERIT Study). *AJNR Am J Neuroradiol*. 2012 Jun-Jul;33(6):1050–1058.

AppliedRadiology®
The Journal of Practical Medical Imaging and Management

Anderson Publishing, Ltd
180 Glenside Avenue,
Scotch Plains, NJ 07076
Tel: 908-301-1995
Fax: 908-301-1997
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Editorial Advisory Board

Applied Radiology®

The Journal of Practical Medical Imaging and Management

January / February 2023
Vol 52 No 1

Applied Radiology (ISSN 0160-9963, USPS 943180) is published in print 6 times a year, January, March, May, July, September, and November, by Anderson Publishing Ltd at 180 Glenside Ave., Scotch Plains NJ 07076. Periodicals postage paid at Scotch Plains, NJ and additional mailing offices. Free subscriptions for US-based qualified radiology professionals. Subscriptions for the US and its territories and possessions: $115 per year, $225 for two years. Foreign and Canadian subscriptions $215 for one year payable in US funds, international money orders, or by credit card only. Postmaster: Please send address changes to Applied Radiology, PO Box 317, Lincolnshire, IL 60069-0317 (847-564-5942) or email AppliedRadiology@Omeda.com.

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Call for Service

Erin Simon Schwartz, MD, FACR

Dr Schwartz is the Editor-in-Chief of *Applied Radiology*. She is the Chief of the Division of Neuroradiology and holds the Robert A Zimmerman Chair in Pediatric Neuroradiology in the Department of Radiology at The Children's Hospital of Philadelphia. She is also a Professor of Radiology, Perelman School of Medicine, University of Pennsylvania. She can be reached at erin@appliedradiology.com.

As we open the door to a new year, I am excited to introduce a new section of the Editorial Advisory Board of *Applied Radiology* called, "Early Career Radiologist." Under the direction of Associate Editor Yasha Gupta, MD, this section will focus on matters of practical importance to radiologists-in-training and those still early in their career. A new column will be dedicated to these topics.

Moreover, we want you—the medical students, radiology residents, radiology fellows, and early career radiologists among us—to help fill the section with enthusiastic members and fill the column with valuable content.

Want to volunteer? If you are a medical student interested in radiology, a radiology resident or fellow, or a practicing radiologist less than five years out of training, email me your CV and your best ideas for future columns.

Transitions and Additions

I want to express my gratitude to Kristin K Porter, MD, PhD, as she steps down from her role as associate editor for radiological cases. Dr Porter recently transitioned to private practice, limiting her time for academic pursuits. Thankfully, she has agreed to remain active in the *Applied Radiology* family as a reviewer of case submissions. We value her past and future contributions immensely.

Stepping into this important position is Elizabeth Snyder, MD, assistant professor of radiology and radiological sciences, Vanderbilt University Medical Center, in Nashville, Tennessee. As the new associate editor for radiological cases, Dr Snyder will build upon the infrastructure created by Dr Porter and oversee our transition to a new software platform that promises to streamline the case submission and review process. Dr Snyder will also continue to grow the section with additional reviewers.

Lastly, I am also pleased to announce two more terrific new additions to our Editorial Advisory Board:

- Ryne A Didier, MD, joins our Ultrasound section. Dr Didier is a pediatric radiologist and fetal imager at Boston Children's Hospital and an assistant professor of radiology at Harvard Medical School, Boston, Massachusetts.
- Osman Ahmed, MD, FCIRSE, joins the Interventional Radiology section. Dr Ahmed is an interventional radiologist, director of venous interventions, and associate professor of radiology at University of Chicago Medicine, Chicago, Illinois.

These are exciting times at *Applied Radiology,* as always. But never before have there been opportunities like these to join our team — especially for radiologists in training. I do hope you will consider participating.

Worrisome and Incidental Signs on Knee Radiographs in Clinical Practice: Traumatic and Degenerative Lesions

Description

A variety of traumatic and degenerative imaging signs are encountered in daily clinical practice on knee radiographs. Knowledge of their clinical presentations, imaging characteristics and outcomes helps to inform radiologists when additional imaging is needed or to bestow confidence when further work is not required. This activity is designed to educate radiologists and radiologists in training about worrisome traumatic imaging signs, and incidental degenerative and developmental diagnoses, on knee radiographs to help guide clinical management

Learning Objectives

Upon completing this activity, the reader should be able to:

- Describe worrisome radiographic signs for traumatic knee injuries.
- Discuss degenerative and developmental signs on knee radiographs.
- Explain when additional cross-sectional imaging may help guide clinical management.

Target Audience

- Radiologists
- Related Imaging Professionals

Authors

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Commercial Support

None

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Expiration date: Dec. 31, 2024

Disclosures

Planner: Erin Simon Schwartz, MD, FACR, discloses no relevant financial relationships with any ineligible companies.

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Worrisome and Incidental Signs on Knee Radiographs in Clinical Practice: Traumatic and Degenerative Lesions

Irina Kapustina, MD, PhD; George Morcos, MD; Mark Wieland, MD; Derik L Davis, MD

Editor's note: This is the first part of a two-part series. The second part will appear in the March/April 2023 issue of Applied Radiology.

Most diagnostic errors by radiologists in clinical practice involve musculoskeletal findings on radiographs, and missed fractures represent more than 90% of malpractice claims.[1,2]

Knee radiography is one of the most common musculoskeletal studies interpreted by radiologists in daily clinical practice and is the standard of care for initial imaging of acute or chronic knee pathology.[3-5] A variety of knee radiography protocols exist, but every study should at minimum contain frontal (anteroposterior [AP] or posteroanterior) and lateral views.[4] Other common options in a knee radiograph series include weight-bearing, patellar tangential, oblique, and cross-table lateral views.[4,6,7]

In this article we describe worrisome imaging signs on knee radiographs to inform radiologists and radiologists-in-training how to identify a select group of difficult-to-diagnose traumatic pathologies and when to recommend additional imaging or clinical work up. We also discuss incidental signs of degenerative joint disease and a developmental anomaly on knee radiographs that mimics worrisome pathology, in order to allow definitive diagnosis and to bestow confidence that no further work up is required.

Affiliation: University of Maryland School of Medicine, Baltimore, Maryland.
Prior publication/presentation: Davis DL. Let's get ready to rumble: incidentalomas versus not-so-incidental findings on knee radiographs (electronic exhibit). American Roentgen Ray Society 2014 Annual Meeting, San Diego, California, May 4-9, 2014.

Traumatic Fractures

Segond Fracture

The Segond fracture is important to recognize due to its strong association with anterior cruciate ligament (ACL) and meniscal tears.[8] The typical mechanism involves excessive internal rotation and varus stress, which cause a focal avulsion of bone from the lateral tibial plateau, commonly sustained as a sports-related injury. Patients commonly present with acute knee pain.[9]

On radiographs, the Segond fracture appears as a small, avulsed bone fragment from the lateral tibial plateau (Figure 1). Although the injury is subtle in appearance on radiographs, magnetic resonance imaging (MRI) demonstrates the strong association with ACL tear to greater detail).[7] The primary emphasis is placed on surgical intervention for the underlying knee internal derangement.[10]

Tibial Spine Fracture

Tibial spine fractures most often occur in skeletally immature knees. This injury is considered equivalent to adult ACL tears, as children and adolescents have a greater propensity to suffer acute bone injury from ACL avulsion of the tibial spines rather than ligamentous tear of the ACL as compared to adults.[11] Mechanisms for injury include abnormal knee rotation or blunt trauma near the anterior knee while the joint is flexed. Patients typically present with pain, swelling, and decreased range of motion.[12]

Tibial spine fractures appear through the central region of the proximal tibia epiphysis, often with an associated knee joint effusion (Figure 2). Computed tomography (CT) and MRI have greater sensitivity to delineate fracture characteristics, while MRI can also be used to diagnosis additional meniscal, ligamentous, and/or articular cartilage internal derangements relevant for preoperative planning.[11] Treatment of these fractures with ACL avulsion typically consists of surgery or casting in the pediatric population.[11]

Lipohemarthrosis

In the acutely traumatized knee, systematic evaluation of the soft tissues is required. Lipohemarthrosis, defined as intra-articular floating fat in a joint effusion, is an important clue for diagnosing radiographically-occult fractures.[6,13] Traumatic intra-articular fracture is the primary mechanism

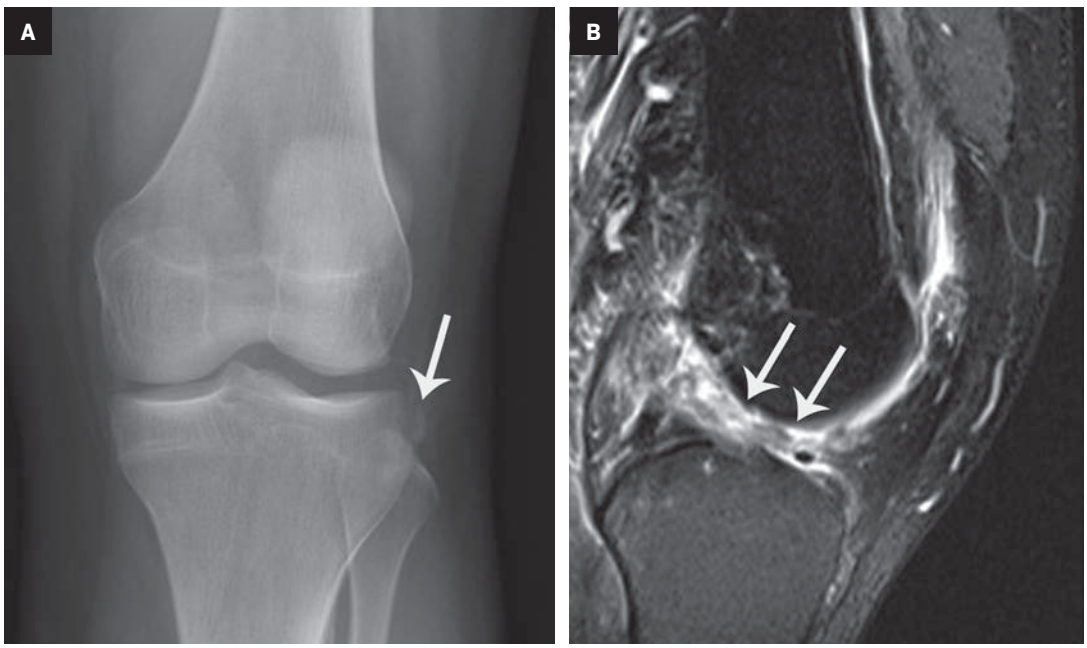
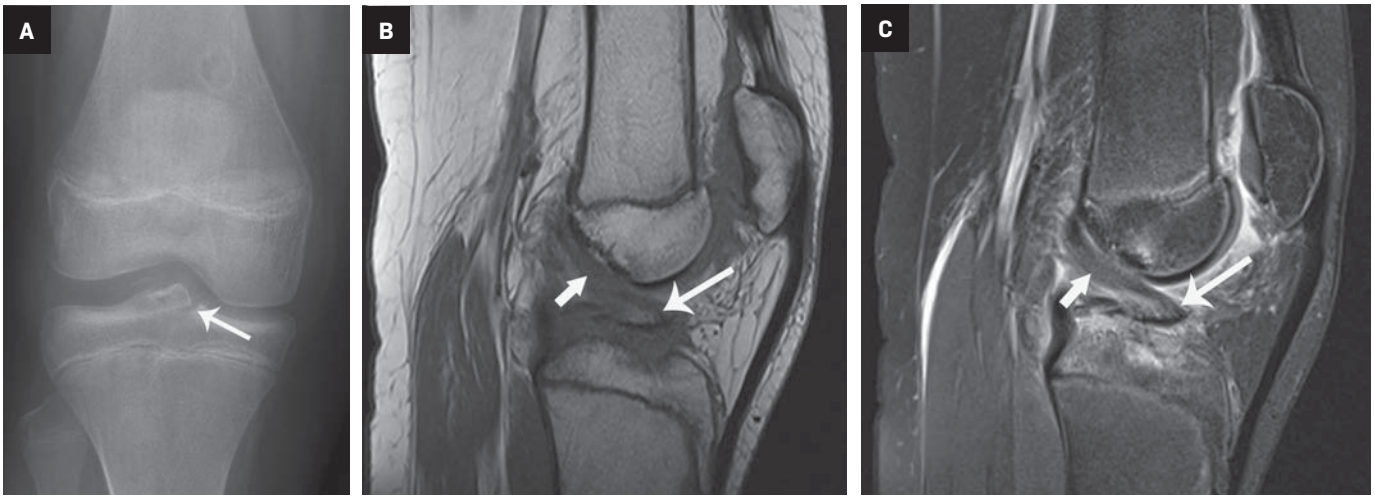


Figure 1. Segond fracture. (A) AP radiograph shows a mildly displaced acute fracture fragment (arrow) from the lateral aspect of the lateral tibial plateau in a patient presenting with acute knee trauma. (B) Sagittal T2 fat-saturated MRI shows an absence of the anterior cruciate ligament at the intracondylar notch (arrows) compatible with complete tear.

Figure 2. Tibia spine fracture. (A) AP radiograph shows a mildly displaced transverse acute fracture at the tibial spine region (arrow) of the proximal tibial epiphysis in a skeletally immature patient. There is also a nonossifying fibroma incidentally noted at the distal femoral metadiaphysis. (B) Sagittal T1 and (C) sagittal T2 fat-saturated MR images show the anterior cruciate ligament (short arrow) attached to the avulsed tibial spine fracture (long arrow) with associated bone marrow edema.



for fatty marrow leakage into the joint space and lipohemarthrosis is pathognomonic for acute fracture.[6,14] Acute pain and swelling are classic symptoms/signs.

Radiologists should consider cross-table lateral radiographs for all traumatic knee series, as standard frontal and lateral views are less likely to identify lipohemarthrosis.[6,15] On cross-table lateral views, the key finding is a sharp linear interface between hydrophobic floating fat and hydrophilic hemarthrosis, most commonly seen at the suprapatellar pouch (Figure 3). Occasionally, lipohemarthrosis will present with three distinct layers when the hemarthrosis further separates into distinct serum and red blood cell layers.[6,16] In the setting of lipohemarthrosis without a definite radiographically visible fracture, the radiologist should inform the exam requestor that additional cross-sectional imaging is indicated to detect and characterize the occult fracture.[17] Treatment is typically driven by orthopedic management of the underlying fracture, with self-resolution of the lipohemarthrosis.

Traumatic Malalignment

Anterior tibial translation

Anterior tibial translation (ATT) is an important radiographic sign of knee instability.[18] The ACL primarily

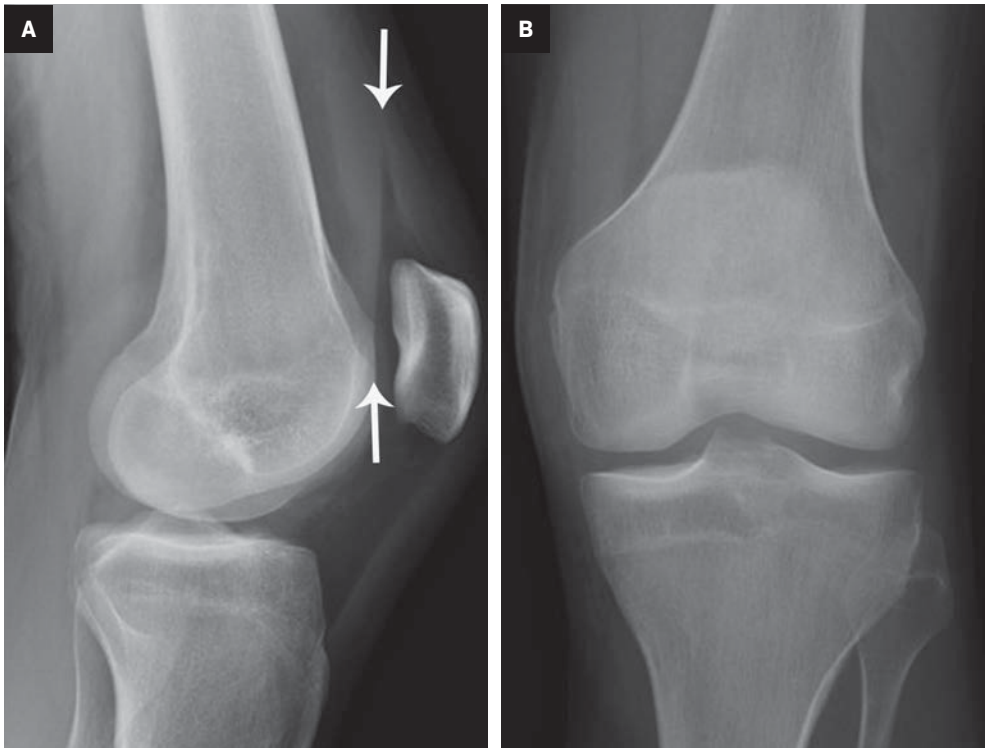


Figure 3. Lipohemarthrosis. (A) Cross-table lateral and (B) AP radiographs show no obvious fracture in a patient with blunt trauma to the knee after a fall. The sharp interface produced by the fat-fluid level (between arrows) reflects a lipohemarthrosis owing to an acute occult fracture, indicating the need for follow-up with cross-section imaging.

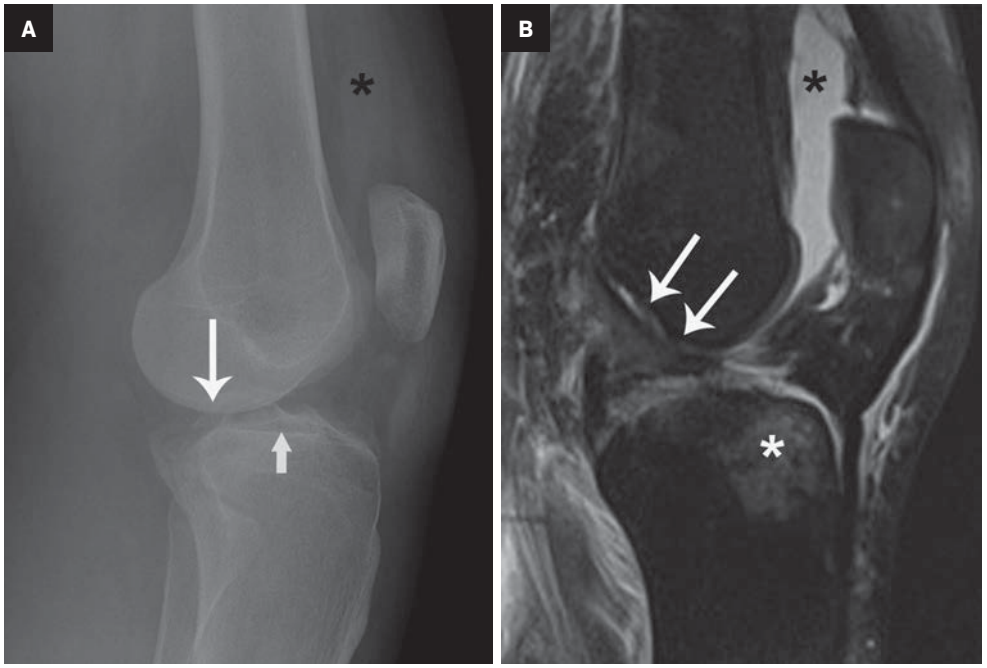


Figure 4. Anterior tibial translation. (A) Lateral radiograph from a pedestrian struck by a car shows a suprapatellar knee effusion (black asterisk). The center of the femoral condyles (long arrow) articulates with the posterior third of the tibial plateau instead of the center (short arrow). (B) Sagittal T2 fat-saturated MR image shows an absence of the anterior cruciate ligament at the intracondylar notch (arrows) compatible with complete tear. An acute bone contusion is present at the tibia (white asterisk).

resists ATT but when torn allows abnormal anterior subluxation of the tibia relative to the femur.[19,20] In the acute clinical setting, severe pain and swelling are common. In cases of subacute clinical presentation, perceived instability may be the most pressing concern.[21]

On a lateral knee radiograph, ATT appears as the central region of the femoral condyles articulating with the posterior third of the proximal tibial plateau (Figure 4). In this setting, MRI may be considered to definitively characterize the ACL tear and identify other potential injuries. Treatment is based on orthopedic management of the tear and any other associated internal derangements.

Patella Alta

Patella alta is a "high-riding" patella that rests in a more proximal position than expected relative to

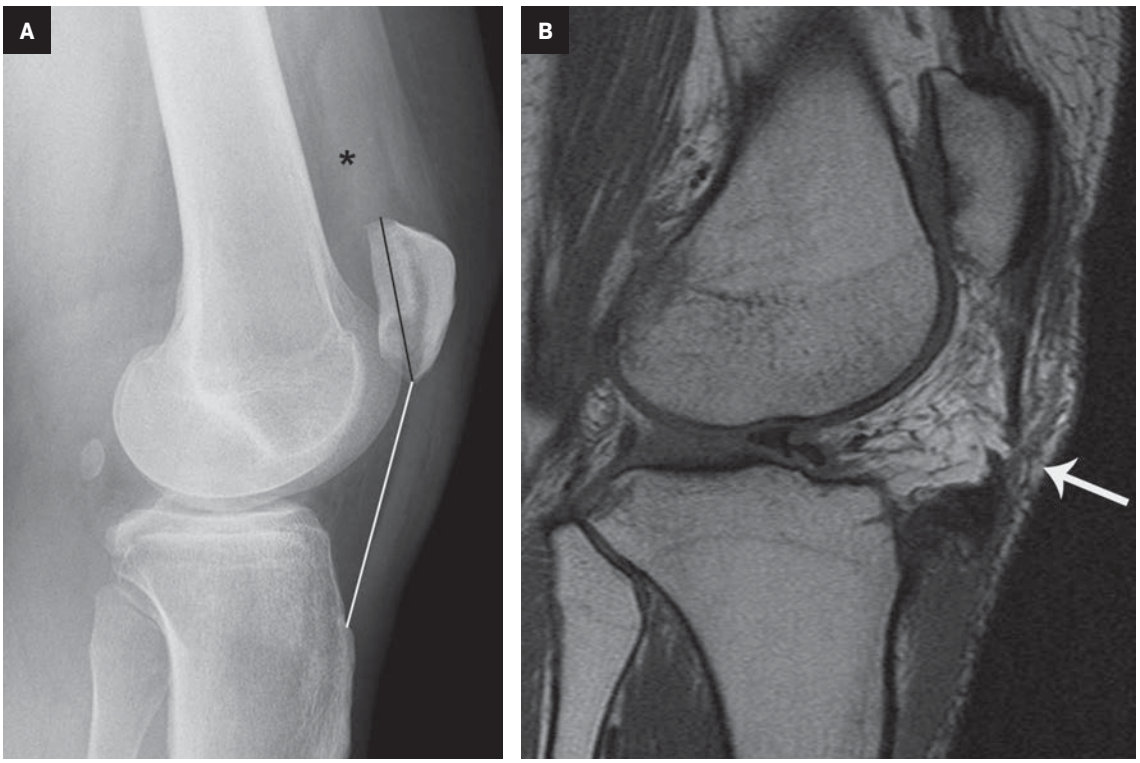
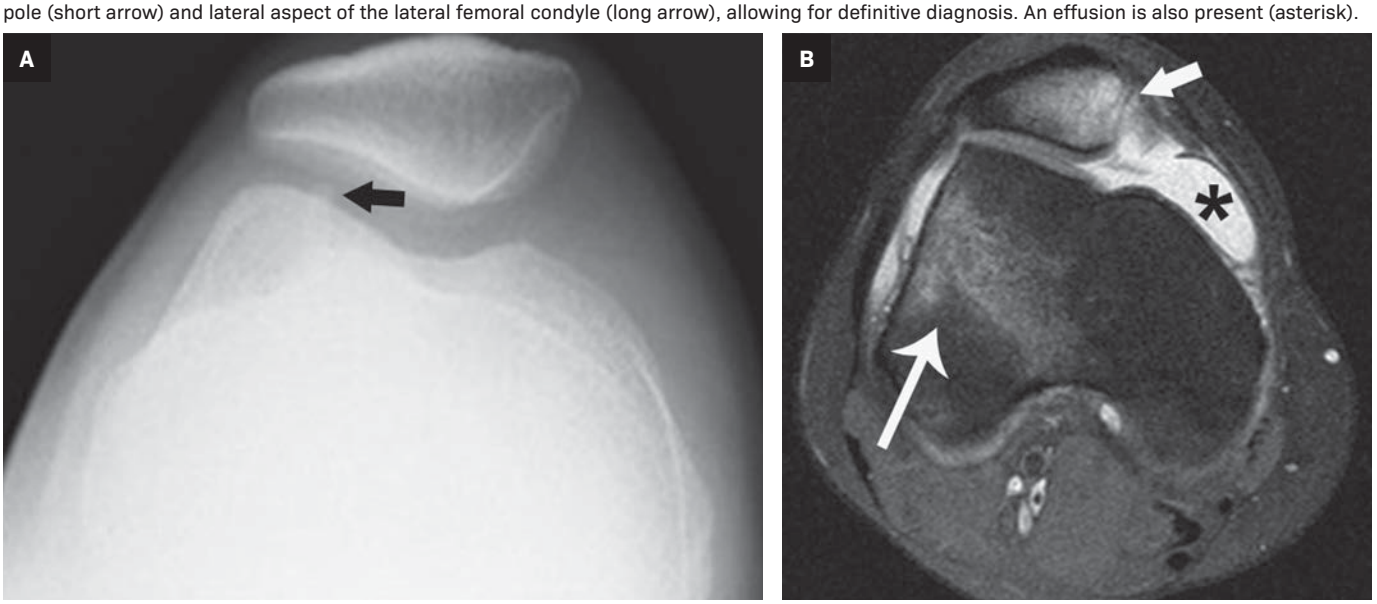


Figure 5. Patella alta. (A) Lateral radiograph of a patient with acute blunt trauma from a fall shows a knee effusion (asterisk) and a > 20% difference (ratio > 1.2) between the maximum oblique distance across the patella (black line, 4.5 cm) and the distance from the patellar inferior pole to tibial tuberosity (white line, 7.0 cm). (B) Sagittal T1 MR image shows an acute patellar tendon tear (arrow).

Figure 6. Transient patellar dislocation. (A) Sunrise radiograph of a patient with pain and instability shows a small ossific fragment (arrow) in the patellofemoral compartment. (B) Axial T2 fat saturated MR image shows the classic bone marrow contusion pattern centered at the medial patellar pole (short arrow) and lateral aspect of the lateral femoral condyle (long arrow), allowing for definitive diagnosis. An effusion is also present (asterisk).



the tibiofemoral articulation. Most cases represent a developmental anomaly, but acquired patella alta is suspicious for a ruptured patellar tendon. Acutely acquired patella alta typically presents with new-onset knee pain, swelling, and decreased range of motion.[22,23] Chronic patella alta presents with a more insidious onset of patellofemoral pain and recurrent patellar subluxation or dislocation.[24,25]

Patella alta is most commonly evaluated on the lateral knee radiograph using the Insall-Salvati method (Figure 5). Patella alta is diagnosed when the distance from the inferior pole of the patella to tibial tuberosity is more than 20% of the maximum oblique distance across the patella.[26] Thus, a ratio of more than 1.2 indicates patella alta on a lateral knee radiograph. The condition is managed orthopedically

Figure 7. Osteochondritis dissecans. (A) AP radiograph demonstrates a discrete curvilinear lucency (arrow) with an adjacent small, ovoid ossific fragment at the lateral aspect of the medial femoral condyle. (B) Coronal proton density and (C) sagittal short tau inversion recovery MR images demonstrate fluid signal (long arrow, B) completely separates the in-situ fragment (short arrow, C) from the medial femoral condyle.

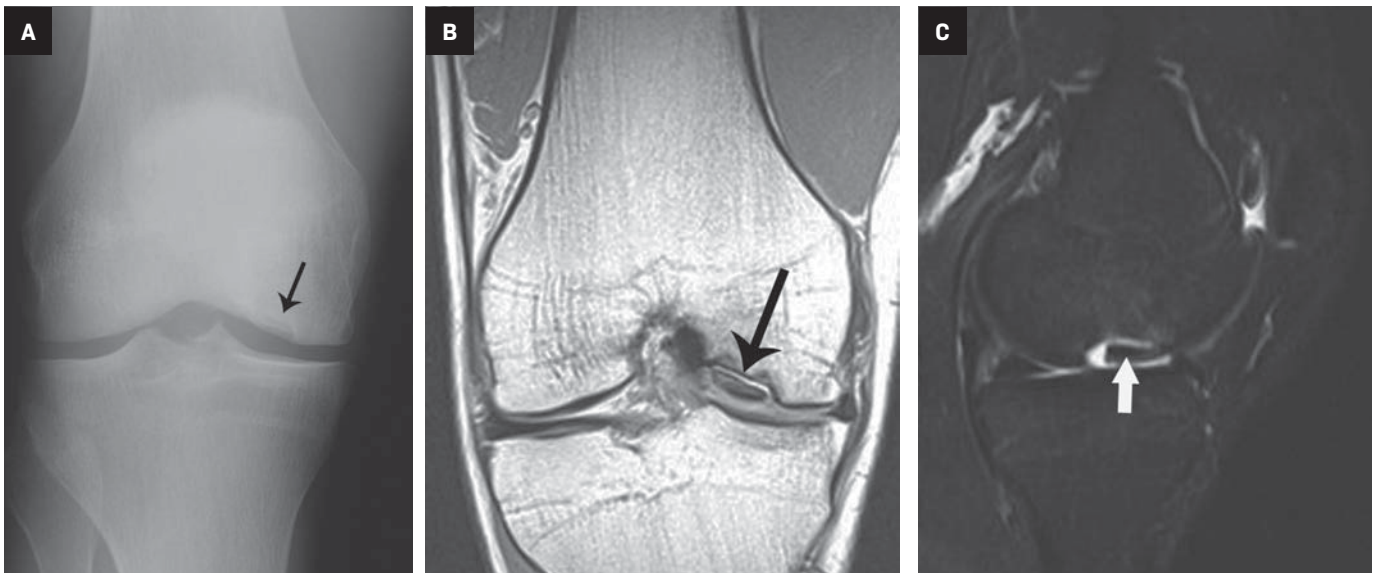
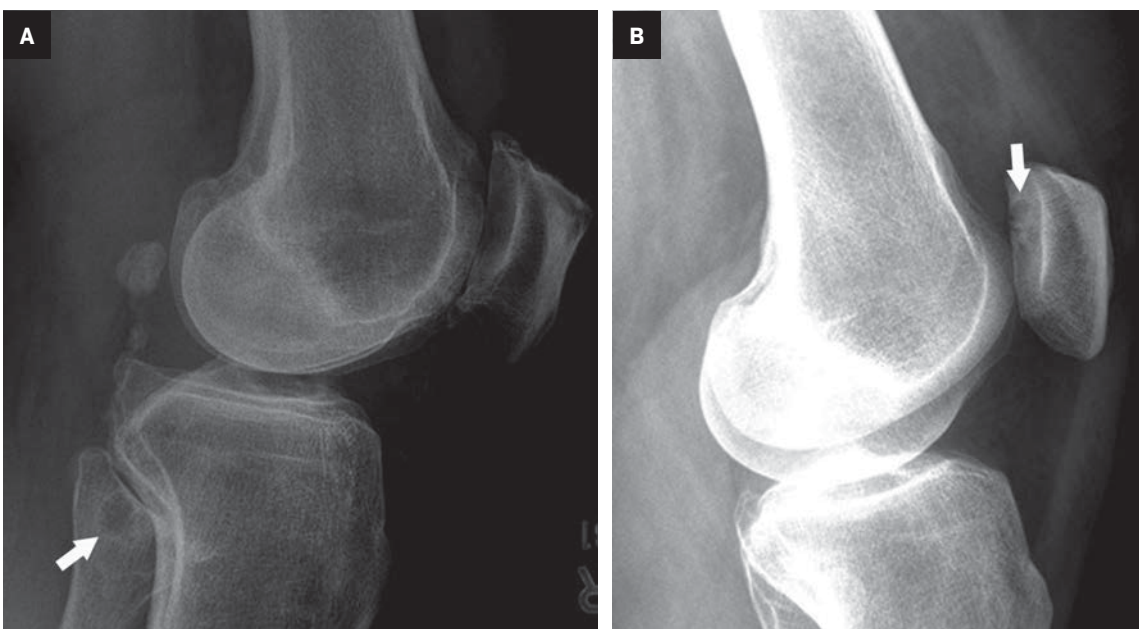


Figure 8. Geode. (A) Lateral view shows a small, round, linear lucency with a thin sclerotic margin (arrow) in the fibular head. Proximity to the proximal tibiofibular joint allows for the diagnosis of a benign geode. (B) Lateral view in a different patient shows an isolated focal lytic lesion with a narrow zone of transition at the articular surface of the patella (arrow) consistent with a geode.



on a case-by-case basis, depending on the underlying cause and presenting symptoms.[27]

Transient Patellar Dislocation

Transient patellar dislocation (TPD) is a knee instability syndrome affecting the patellofemoral compartment. The term "transient" implies brief events of lateral patellar subluxation or dislocation followed by spontaneous reduction.[28,29] Although TPD may occur at any age, adolescents and young adults classically are most affected. Patients often present with knee pain and a history of patellar dislocation with spontaneous reduction. Clinically, TPD is elusive, and more than 50% of cases are initially clinically misdiagnosed.[28]

Radiographic diagnosis of TPD may be challenging, since most spontaneously reduce prior to imaging. A high clinical suspicion and correlation with clinical history increase the probability of diagnosing this abnormality. Detecting an osseous fragment in the suprapatellar joint space may provide the only perceptible clue (Figure 6). Most cases often present with a nonspecific joint effusion.[30] MRI evaluation can "rule in" TPD, since the modality allows for identification of the classic "kissing contusion" bone marrow edema pattern located at the medial patellar

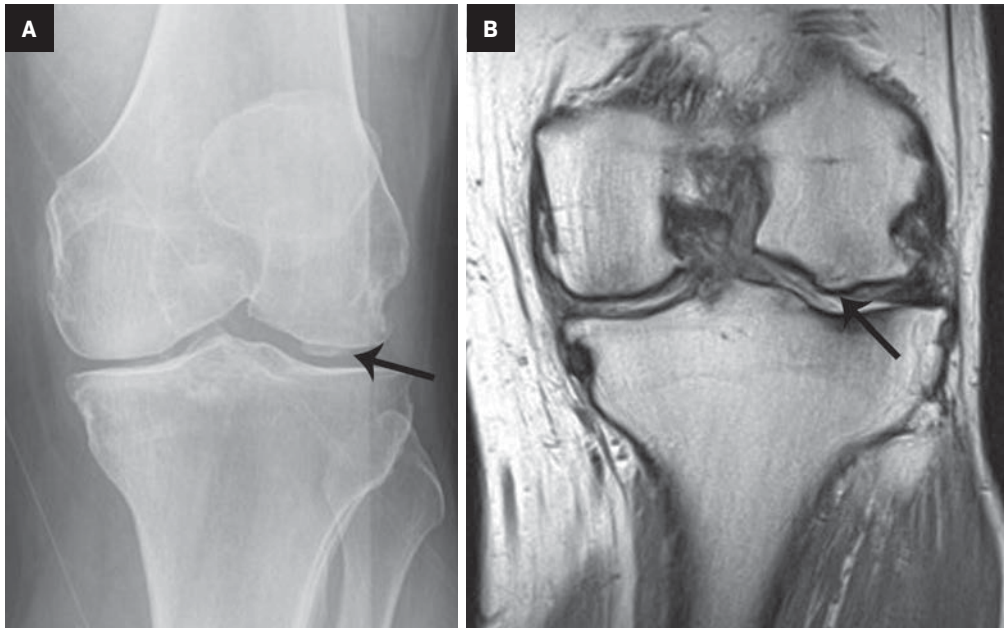


Figure 9. Central osteophyte. (A) AP view in a patient with signs of degenerative joint space narrowing and small marginal osteophyte formation with a small osseous protuberance at the central articular surface of the lateral femoral condyle (arrow). (B) Coronal proton density MRI image shows an osseous protuberance (arrow) in continuity with the subchondral bone and without overlying articular cartilage, consistent with a central osteophyte.

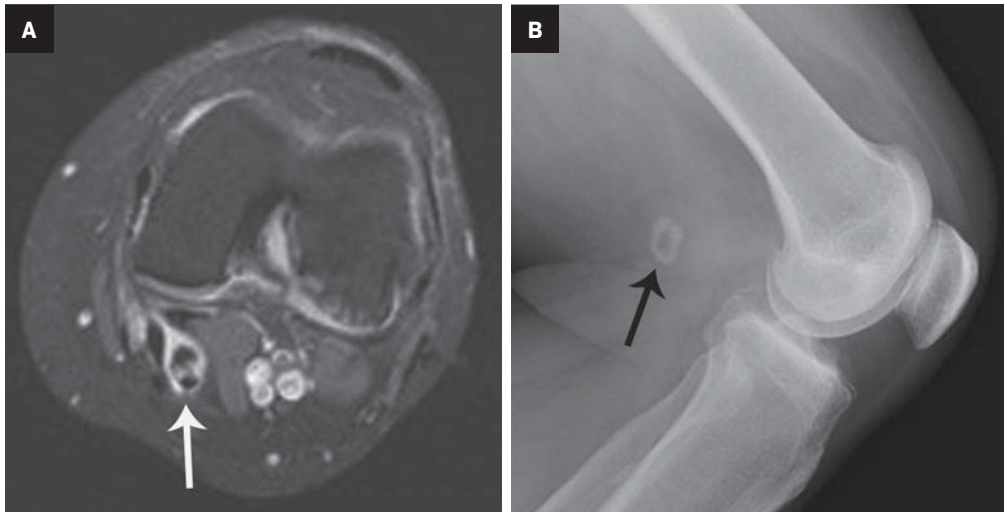


Figure 10. Baker cyst osteochondral body. (A) Lateral radiograph shows an osteochondral body (arrow) with peripheral mineralization in the soft tissues of the posterior knee. (B) Axial proton density fat saturated MR image shows the osteochondral body located inside of a Baker cyst.

pole and lateral femoral condyle (Figure 6). Corrective surgery to address predisposing ligamentous and osseous abnormalities is performed in knees deemed unstable.[28,31]

Miscellaneous Worrisome Mimics

Osteochondritis dissecans

Osteochondritis dissecans (OD) is a chronic disease of subchondral bone that can mimic signs of fracture on knee radiographs, most commonly in the lateral region of the medial femoral condyle. Adolescents and young adults are the most likely to manifest OD, often presenting with knee pain, swelling, and locking.[32] Identifying advanced-stage OD before the in-situ bone fragment displaces into the joint space improves long-term prognosis.

Radiographic findings of advanced OD with an in situ fragment demonstrates an ossific fragment at the articular surface, separated from the adjacent bone by a curvilinear lucency (Figure 7). Its location at the lateral region of the medial femoral condyle and relative smooth margins of the curvilinear lucency help to differentiate OD from an acute fracture. MRI can confirm the diagnosis and provide staging information critical for treatment. Patients with unstable in-situ fragments are candidates for surgery.[32,33]

Incidental Signs

Degenerative Joint Disease

Geode

A geode is a subchondral cyst typically associated with full-thickness articular cartilage loss. Geodes are

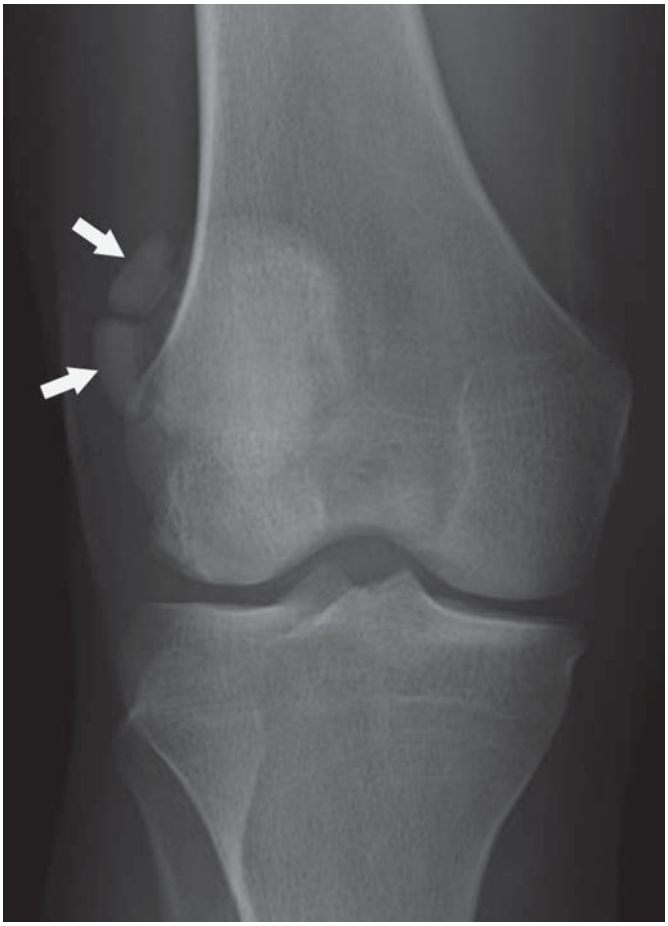


Figure 11. Multi-partite patella. AP radiograph shows two well-defined, non-united ossified secondary ossification centers at the superolateral pole of the patella, consistent with a tri-partite patella.

not true "cysts" but instead represent cyst-like changes. Most cases do not represent a diagnostic dilemma for the radiologist, since they typically present with other findings related to osteoarthritis – including osteophytes, joint space loss, and/or subchondral sclerosis.[34-36] Symptomatic patients often present with complaints emblematic of osteoarthritis – knee pain, stiffness, and swelling, among others. However, geodes presenting on radiographs in isolation without other definitive signs of osteoarthritis may be confused with more worrisome diagnoses such as malignancy.

Radiography demonstrates geodes as classically round, well-defined, lytic lesions with a thin, sclerotic, narrow zone of transition at an articular surface (Figure 8). Their location at the subchondral bone of an articular surface and appearance should allow for confident radiographic diagnosis of a benign, degenerative geode requiring no additional follow-up.

Central Osteophyte

Osteoarthritis is commonly diagnosed in patients who present clinically with variable complaints of knee pain, swelling, locking, and stiffness**.** The osteophyte is a basic feature in establishing the radiographic diagnosis, with osteophyte formation typically occurring at the joint margins. The precise pathogenesis of osteophytes is still unclear but is thought to represent a response to altered biomechanics.[37] Osteophytes that occur at the center, rather than at the margin, of the joint are much less common.[38,39] Radiologists should not confuse central osteophytes with truly worrisome bone conditions.

On radiographs central osteophytes appear as well-defined focal osseous protuberances in continuity with the subchondral bone at the articular surface (Figure 9). Associated signs of osteoarthritis – marginal osteophytes, joint-space narrowing, and/or geodes – should increase diagnostic confidence for a degenerative central osteophyte requiring no additional work up.

Baker Cyst Osteochondral Body

Degenerative intra-articular osteochondral bodies ("loose bodies") are a well-known condition in patients with knee osteoarthritis. On radiographs, a mineralized mass centered in the soft tissues rather than in the knee joint raises potential suspicion for malignancy. Baker cysts are synovial cysts created by a region of the posterior knee joint capsule that anatomically has displaced in a posterior direction between the semimembranosus and medial

head of the gastrocnemius tendons. Typically, joint contents travel into the Baker cyst through a mechanism resembling a one-way valve.[35] Displaced osteochondral bodies, and even meniscal fragments, are known to collect in Baker cysts.

Radiographically, single or multiple well-defined osteochondral bodies appear as one or more mineralized masses in the soft tissues behind the knee (Figure 10). Identifying additional findings associated with osteoarthritis — osteophytes, joint space loss, geodes, and/or subchondral sclerosis — should allow more confident diagnosis of degenerative osteochondral bodies in a Baker cyst without the need for follow up. Radiographs that lack any other signs of osteoarthritis, have an ill-defined or stippled pattern of mineralization, or show an unexplained mineralized soft-tissue mass in a location not consistent with a Baker cyst should undergo cross-sectional imaging to exclude malignancy or other worrisome conditions.[35,40]

Miscellaneous (Incidental)

Multi-partite Patella

Developmental anomalies of the patella are common. The patella is the largest sesamoid bone in the body with variable fusion patterns of secondary ossification centers. The most common location is the superolateral pole.[41,42] Particularly in the setting of trauma, multi-partite patella can create diagnostic uncertainty on radiographs by mimicking the appearance of acute fracture.

Multi-partite patella can be differentiated from a comminuted fracture by identifying two or more smooth, well-defined, and non-united round or ovoid secondary ossification centers located at the superolateral pole and separated from each other and the larger patellar body by well-defined curvilinear lucencies (Figure 11).[41-43] In the absence of associated bony tenderness with direct palpation at the site of a classically-appearing multi-partite patella on physical examination, no follow up is necessary.

Conclusion

Knee radiography is common in daily clinical practice. Knowledge of worrisome signs related to difficult-to-detect traumatic knee pathology informs radiologists when to expeditiously recommend additional imaging and/or clinical evaluation.

Familiarity with less-common incidental signs of degenerative joint disease and developmental anomaly allow for definitive diagnosis and confidence that no further evaluation is required.

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Giant Sigmoid Diverticulum: Imaging Features and Management

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Diverticular disorders of the colon are common among the aging population of industrial countries. About 50% of individuals older than 60 years of age develop diverticulosis predominantly involving the sigmoid, and 10-20% of them will experience complications during their lifetime, such as diverticulitis, hemorrhage, perforation and fistula to the adjacent organs.[1,2] However, a giant sigmoid diverticulum (GSD) is a rare complication and may present a diagnostic and therapeutic challenge for those who are unfamiliar with the condition.[3-6]

The majority of publications about GSD have been isolated case reports in the surgical literature. This article reviews the imaging and management of GSD.

Radiographic Findings

Abdominal radiographs reveal the appearance of a GSD as a round or oval, gas-filled structure in middle or left side of the abdomen, usually measuring from 5 to 12 cm in maximal diameter. Colonic examination with contrast enema can demonstrate partial opacification in most patients (Figures 1, 2). In some instances, however, barium may not enter the GSD on either the colon study or per-oral administration of contrast material. On rare occasions multiple giant sigmoid diverticula may be encountered in the same patient. GSD is associated with comorbid diverticulosis.

Abdominal Computed Tomography Findings

The initial diagnosis of GSD is often made on computed tomography (CT) of patients with a history of diverticular disease and present with recurrent symptoms. GSD appears as a gas-filled mass with thin walls of about 1 mm, or as a thick-walled cavity containing gas and fluid in some other patients (Figures 2-5). The connection with the colonic lumen may not visible unless rectal contrast is administered.

Therapeutic Management

Segmental resection of the sigmoid with the attached GSD is usually performed by open laparotomy or laparoscopic surgery in most patients. The pathological specimens show that the GSD protrudes from the anti-mesenteric aspect of the sigmoid, and most have inflamed and thickened walls associated with adjacent chronic diverticulitis. Acute diverticulitis is usually treated conservatively rather than by prophylactic sigmoidectomy.

Interventional radiologists treat some patients with GSD via percutaneous drainage, typically under CT guidance. During this procedure, a needle is inserted to suction any fluid content, and then replaced by a pigtail catheter for external bag drainage (Figures 4, 5). Follow-up CT usually shows gradual collapse of the lesion over 4-6 weeks. No recurrence of GSD was detected during 3 years of observation in four cases treated by this technique at our institution.

Radiologic-Pathologic Correlation

Based on the appearance of GSD on imaging studies and pathologic specimens, two patterns can be identified.

Type 1 includes cases whereby the GSD has thin walls (about 1 mm) on CT, protrudes into the pericolic region beneath the serosal layer, and harbors no inflammatory changes within it or the surrounding tissue. This type results from progressive distention of a pulsion diverticulum, where its narrowed neck serves as a unidirectional valve, thus permitting passage

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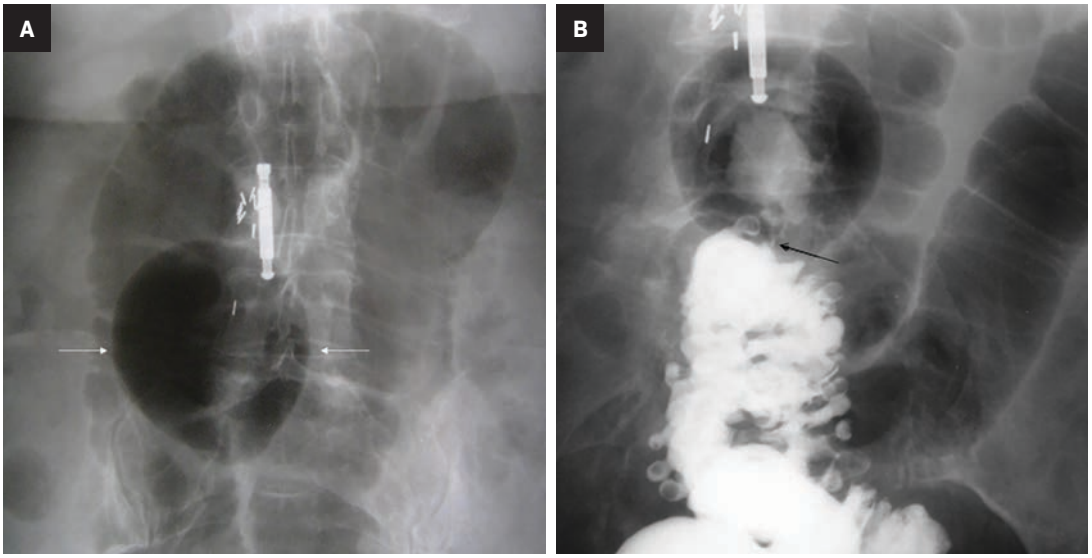
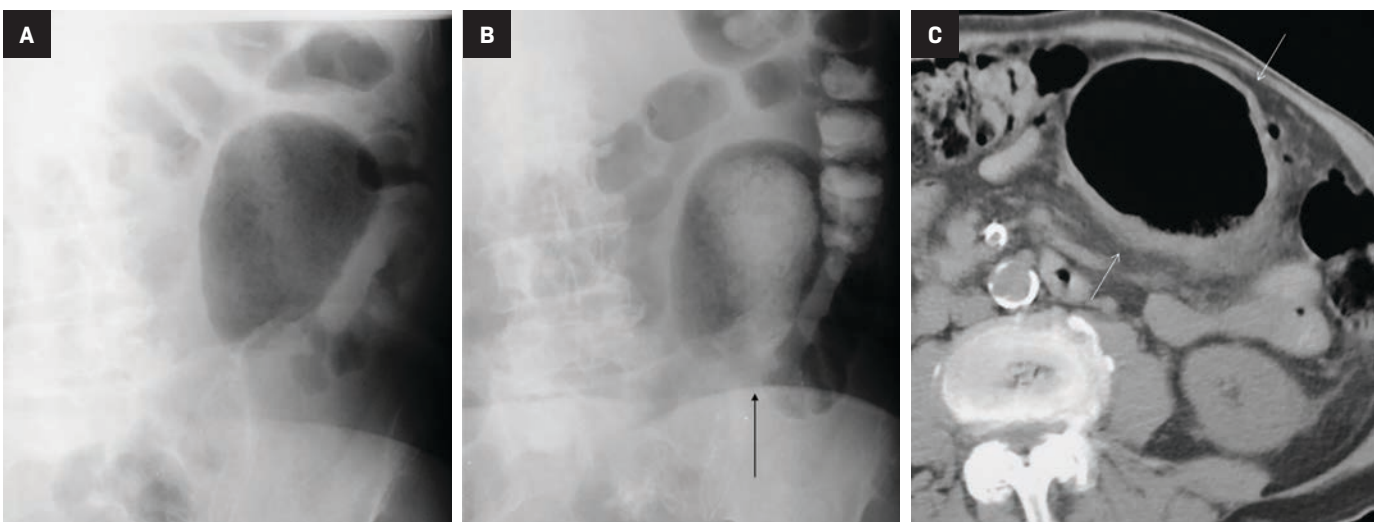


Figure 1. Giant sigmoid diverticulum in an elderly adult (with spinal stimulation device). (A) Abdominal radiograph shows a 5 cm round, gas-filled structure in the mid-abdomen (white arrows). (B) Barium enema examination reveals its narrow connection to the sigmoid colon involved by diverticulosis (black arrow).

Figure 2. Radiological appearance of a GSD in an elderly adult. (A) Abdominal film demonstrates 6 cm, oval-shaped gas collection. (B) Iodinated contrast enema shows partial opacification from its connection to the sigmoid (arrow). (C) CT examination 9 months later reveals slight enlargement of this GSD and thickening of its wall (arrows). This patient underwent laparoscopic resection of the sigmoid colon.



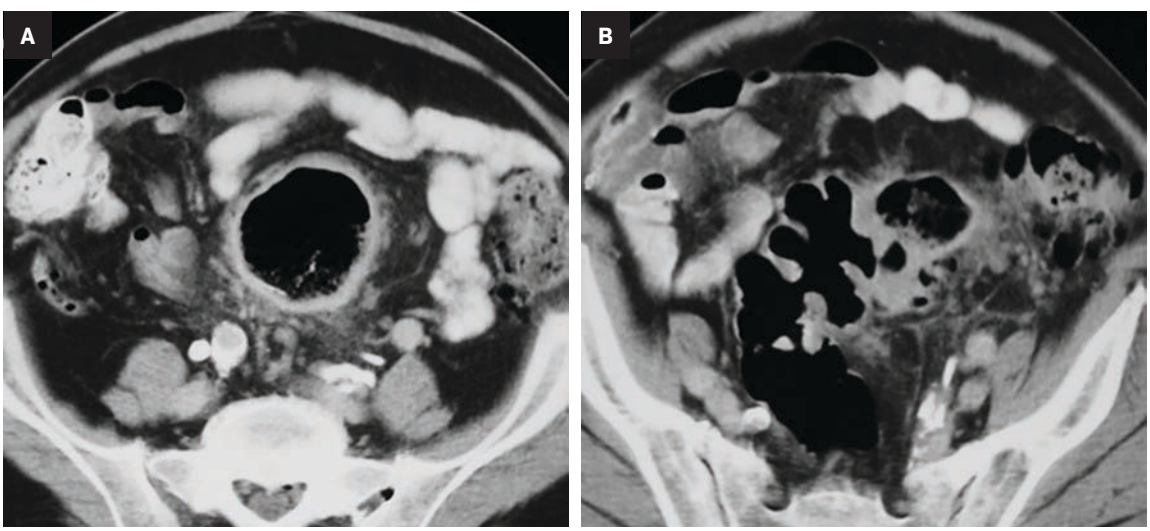


Figure 3. (A,B) CT of the abdomen in an elderly adult demonstrates the GSD as a gas-filled cavity with thick walls, associated with sigmoid diverticulitis.

Figure 4. Interventional radiologic management of GSD in an adult. (A) CT shows a 6 cm cystic lesion with 2-mm-thick walls, containing gas and fluid. The adjacent mesenteric fat has vascular engorgement and edema due to inflammation. (B) CT-guided placement of a pigtail catheter into the lesion. External drainage led to its gradual collapse. (C) CT performed 2 months later shows reduced size of the GSD to about 2 cm (arrow), which resolved on follow-up studies.

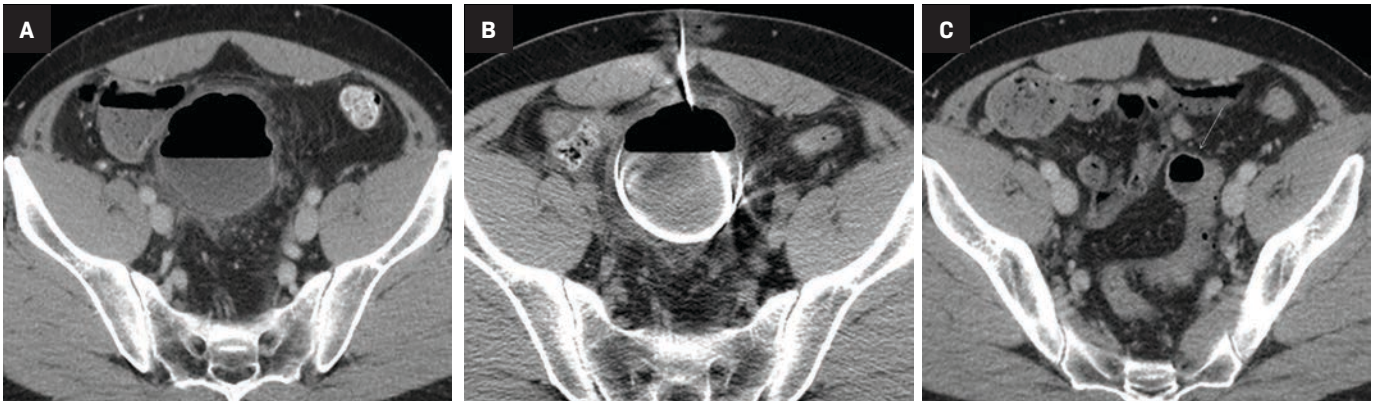
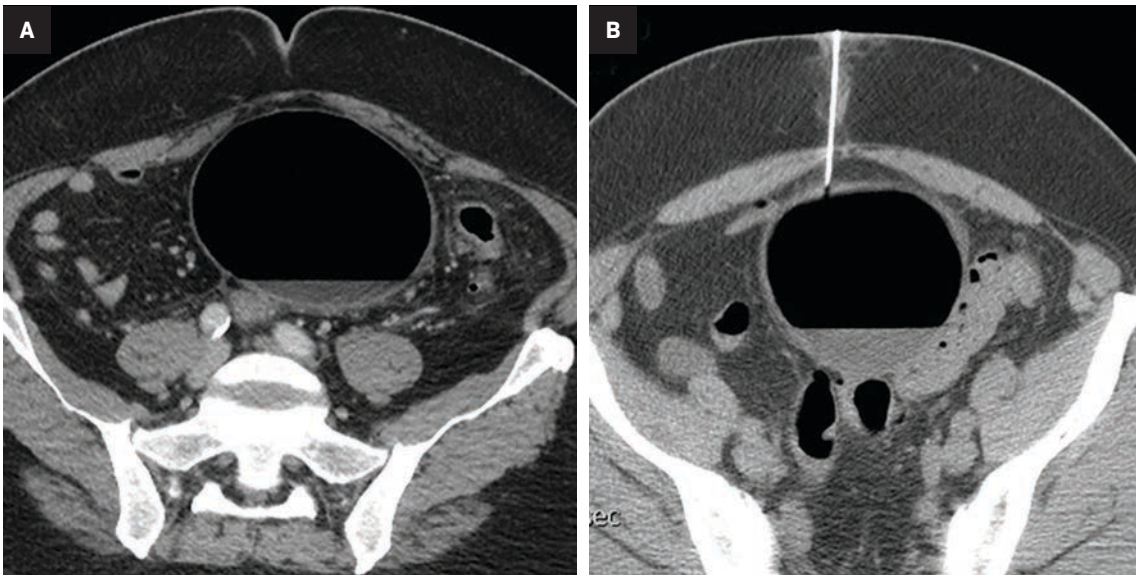


Figure 5. (A) CT of the abdomen in a middle-aged adult reveals a 9 cm GSD with very thin walls. (B) CT-guided needle insertion into the lesion prior to placing a pigtail catheter. Drainage of gas and sero-sanguinous fluid reduced the lesion and led to its resolution.



of colonic gas and its entrapment within the diverticular lumen (Figure 6). Such a pulsion diverticulum can result from a focal outpouching of the wall caused by elevated intraluminal pressure. Although the walls of GSD are originally composed of intact colonic mucosa and submucosal layers, they may be later replaced by fibrotic tissue.

Type 2 consists of GSD cases with irregular and thickened walls, associated with inflammation both in the diverticulum and the attached segment of sigmoid colon (Figure 6). The underlying pathogenesis is a perforated diverticulitis, causing a peri-colic abscess cavity with fistulous connection to the bowel lumen. The development of anaerobic bacterial infection within the abscess likely contributes to the gas-distended appearance of GSD.

Clinical Implications

Despite the high incidence of diverticular disease among the aging population of the West, GSD are a rather rare complication.[2-5] This pathologic process was first described in the French medical literature in 1946 by Bonvin and Bonte.[7] Another description appeared 6 years later in an English surgical article.[8] A comprehensive review of the world literature was conducted in 2015 by Nigri, et al.[6] Their investigation revealed a total of 166 cases of GSD in 138 publications, with the majority being isolated case reports or small case series. Our experience from a series of 12 cases will bring that total closer to 180. However, it is likely that the GSD will be recognized more frequently in the future owing to the increasing prevalence of diverticular disorders of the colon affecting adult patients.[1-3]

A giant diverticulum may very seldom occur in other segments of the large bowel, such as the transverse colon.[9-11] Furthermore, some of these giant diverticula have been previously called a "solitary air cyst" or "sigmoid pneumatocele."[8, 12, 13]

Figure 6. Diagnostic differentiation of GSD types 1 and 2. (A) Radiograph of the pelvis in a middle-aged adult demonstrates a 5 cm type 1 GSD with thin walls (white arrows). Inset: Histologic section of the deflated diverticulum shows its narrow neck (black arrow) and walls lined by colonic mucosa. (B) CT of the pelvic region in a middle-aged adult shows a type 2 GSD with markedly thickened walls (white arrow). Inset: Pathological specimen of the resected sigmoid colon demonstrates the encapsulated mass with a narrow tract to the colonic lumen (black arrow).

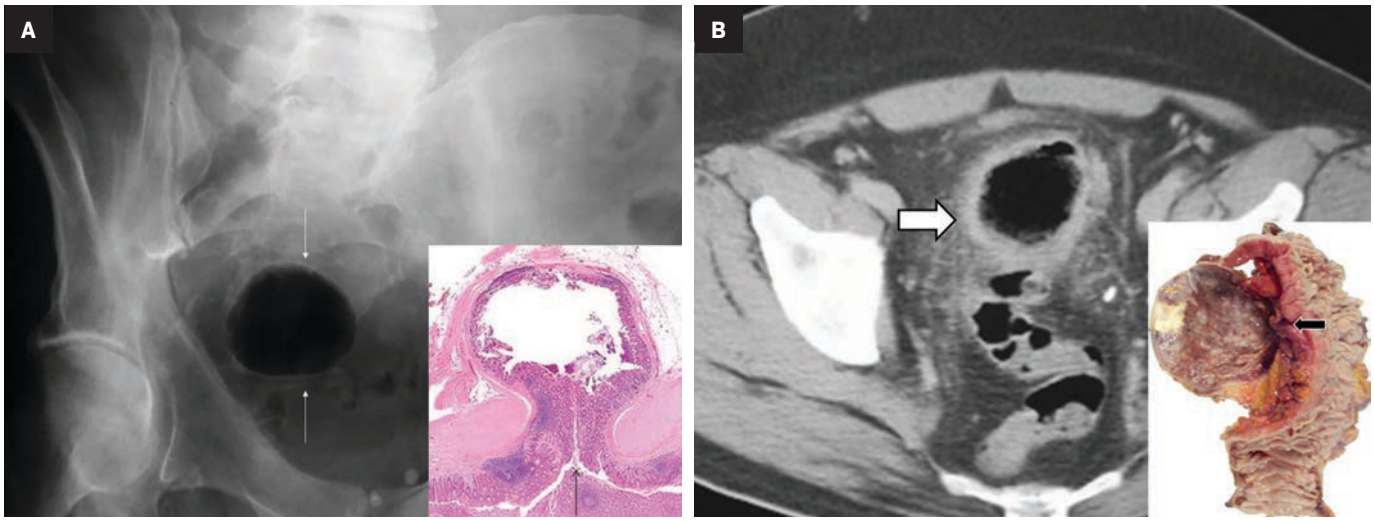
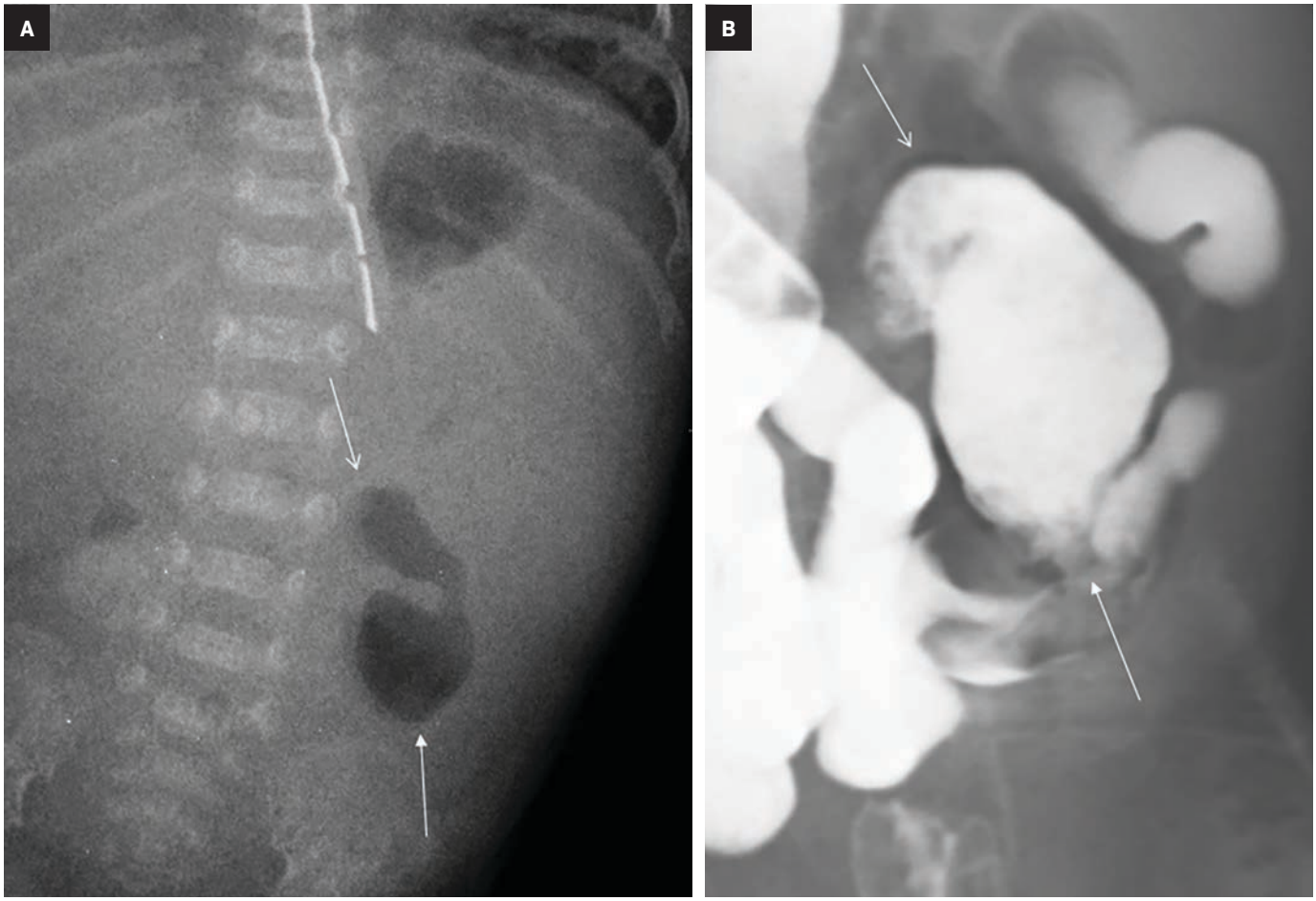


Figure 7. Radiological presentation of a GSD type 3 in a newborn. (A) Abdominal radiograph shows a saccular gas collection in the left lower abdomen (arrows). (B) Barium enema examination reveals a communicating GSD (arrows) which was surgically confirmed.



Three distinct categories of GSD were classified by McNull, et al:[14]

- Type 1 is formed by a diverticulum with thin walls and a narrow neck that allows its inflation with the colonic gas (Figures 1, 2, 5, 6A).
- Type 2 GSD represents a thick-walled abscess cavity resulting from perforated sigmoid diverticulitis (Figures 3, 4, 6B).
- Type 3 is the manifestation of a congenital anomaly, a communicating duplication cyst with all the colonic wall layers. This particular lesion usually manifests in early childhood[15] (Figure 7). Patients with type 1 GSD may be asymptomatic or have only vague abdominal discomfort. Therefore, the lesion may be detected incidentally during radiological examinations for unrelated abdominal conditions. In some instances, a fluctuant mass may be palpable and enlarge with straining or defecation.[2] This lesion may also deflate intermittently and be considered a phantom tumor.[16, 17] In contrast, type 2 GSD is usually associated with clinical symptoms of diverticulitis; thus, these patients will present with abdominal pain and tenderness, fever, and leukocytosis.

The preferred method of treating a GSD is segmental resection with primary colorectal anastomosis. This may be performed through either open laparotomy or laparoscopy.[4, 6, 18] A simple diverticulectomy is rarely done but may be considered in the absence of concomitant colonic diverticular disease.[6]

Patients with type 1 GSD can be treated by CT-guided interventional drain (Figures 5, 6). This method has become a viable alternative to surgery in recent years, and it may be considered for uncomplicated GSD or in patients who are not good candidates for surgery.[19,20]

Some authors have recommended that all patients with GSD undergo prompt treatment to prevent complications such as torsion, volvulus, rupture into the peritoneal space, and malignant transformation.[5, 21]

Differential Diagnosis

The imaging features of GSD are unique, but other pathological processes should also be considered in the differential diagnosis. These include a gas-containing Meckel diverticulum, intestinal duplication cyst, infected pancreatic pseudocyst, necrotic tumor, and tubo-ovarian or intra-abdominal abscess.[2, 22]

Conclusion

Giant sigmoid diverticulum is a rare complication of diverticulosis of the colon in adults beyond their fourth decade of life and is a rarely seen congenital finding in children. The lesion may be asymptomatic and incidental on imaging studies. However, most patients present with symptoms of inflammation. Treatment may benefit from a multidisciplinary surgical and interventional radiology approach.

We may expect GSD to be encountered more frequently in the West, owing to an aging population. Therefore, radiologists, surgeons, and gastroenterologists should be familiar with the imaging features of GSD and its management.

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Mentoring for Success in Academic Radiology

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Mentoring is an increasingly popular and important part of professional development throughout a wide range of fields, including radiology.

Indeed, serving as a mentor is an opportunity to contribute to another person's professional development and to help them perform to the best of their ability. Being a mentee, meanwhile, presents one with an invaluable opportunity to be challenged and guided in setting and achieving professional goals. At its most basic level, mentorship is a partnership; a trusting relationship focused on sharing, and receiving, professional knowledge and experience.

Mentorship, however, is not intended solely for the benefit of the mentee. The ideal mentoring relationship has been described as a shared adventure[1] that can take one or more of several different forms. This article seeks to review some of these arrangements and describe the personal and behavioral characteristics necessary for the establishment of successful professional development relationships.

The term 'mentor' itself derives from the name of an elderly man in Homer's *Odyssey*. Mentor was charged with the important responsibility of caring for and guiding Odysseus' infant son after Odysseus went off to fight in the Trojan War.[2]

Over time, mentoring has come to be recognized as an important component of a wide range of personal and professional relationships. Being a mentor offers opportunities to contribute to another's development. Being a mentee offers opportunities be guided towards goals. For mentor and mentee, mentoring is a two-way partnership that can challenge both to learn and grow while forming a trusted relationship of shared knowledge and experience.

Types of Mentoring Programs

In radiology, the benefits of mentoring are myriad; numerous studies have demonstrated significant benefits of a robust mentoring program tailored to the development of junior faculty.[3-8] Indeed, many radiology departments have developed their own programs.

Some, for example, take the traditional route of establishing "one-on-one" relationships, either through mentees requesting the guidance of a specific faculty mentor, or of departments themselves assigning each new faculty member a career mentor. This model may also sometimes occur in concert with annual group meetings between mentors and mentees, their section/division chiefs, and their department chair to ensure the mentee's academic career is moving toward promotion.

Networking Mentoring

Other mentoring programs, including that of our institution, take the form of mentoring "networks" for junior faculty (Figure).[8] This group model recognizes that there is no such thing as "one size fits all" for good mentoring; that different mentors possess different strengths that can be shared. This model also aims beyond promotion alone as a measure of success to look at overall faculty development, well-being, and integration into the academic community.

In some of these network models, career mentors and mentees are assigned to each other; their relationship is expected to be confidential, and it is understood that their private discussions will be shared with others only under the agreement of both parties. Establishing this confidentiality at the beginning of a mentorship is paramount.

Several other faculty mentor relationships are created and formalized to ensure that faculty are afforded the opportunity for multiple types of mentoring. The mentee remains at the center of this network; they are encouraged to identify and form additional mentor connections that

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Figure. The mentoring model used at our institution under which a network of mentors is assigned to advise and support junior faculty for academic success and career satisfaction.

might help to serve their needs.

Such arrangements further recognize the strength of a community of radiologists in a department, or even across the country, to help build the careers of junior faculty. Indeed, it does "take a village" to nurture the next generation of radiologists.

Types of Mentors

Career Mentor

In this type of mentorship, the mentee is assigned a "career mentor" to foster their professional development. Career mentors are tasked with helping to smooth their mentee's path through academics, to ensure that they become part of the institutional and broader medical community, and to help the mentee learn how to combine career and life goals into their long-term strategy. In this way the career mentor is often the most versatile mentor, serving as coach, guide, motivator, counselor, and confidante.

Obviously, "chemistry" is an important part of mentorship; mentor-mentee matches should be proposed only after consulting with the mentee regarding their needs. Mentors also should be recruited from outside the mentee's intended subspecialty; this is to help prevent the perception of a "power dynamic" in the relationship. It is worth noting that some programs also match for gender and/or race, although some studies suggest that this may not be essential for mentoring success.[9,10]

It is important to ensure mentoring equity. As we work to diversify the junior faculty workforce, the matching expectation can create an unequal burden of mentoring on senior women and other faculty from under-represented groups. Mentoring networks help to reduce this load and also can allow for junior faculty to be mentored by those with different experiences and backgrounds. In our case, we take care to limit the number of mentees assigned to career mentors in order to maintain reasonable time and workload expectations.

Research and Peer Mentors

Two other types of mentors, research and peer, can be important to junior faculty growth. The former collaborate with and guide mentees through idea generation and research supervision and facilitation. Ideally, they push the faculty towards asking and answering original questions that further the radiological knowledge base. They guide, teach, and direct ideas and energies towards academic productivity. They help the mentee learn how to propose, prepare, complete, and publish research projects.

Peer mentors, meanwhile, are faculty at similar stages in their academic career who may be in a different radiologic subspecialty, at another university, or even outside of radiology altogether. Peer mentoring can be informal or formal one-on-one relationships between junior faculty members, or group relationships in which one senior faculty is assigned to a group of junior faculty.[11] Peer mentors are intended to serve more along the lines of coaches, friends, and companions, providing support, advice, and potentially inspiration along the academic journey.

Our institution encourages such cross-specialty and -department relationships by sponsoring workshops and junior faculty breakfasts, albeit significantly hindered during the pandemic. Every mentoring relationship is different but they all serve to support mentee needs. They all also require the mentor and mentee to enter into the relationship in good faith, witha commitment to making the time to connect. Respect is a key ingredient of each relationship.

Co-Mentors

Subspecialty section/division chiefs can serve as "co-career mentors" to help to facilitate the mentoring program, as well as to select and support all types of mentors both within and outside the department. The co-career mentor is also expected to facilitate connections with academic societies to help junior faculty reach national prominence; therefore, serving as a sponsor, manager, guide, and a counselor, along with the other mentors.

Characteristics of Good Mentors

A good mentor brings their experience and knowledge of their specific field and/or the overall workplace environment to their relationship with their mentee. For academic radiologists, this is ideally an associate or full professor with career success, who is highly regarded, and who understands the path ahead for the mentee.

Good mentors are generous with their time and advice, and they provide encouragement, support, and motivation. They provide honest and fair feedback; they are altruistic, understanding, patient, responsive, trustworthy, nonjudgmental, and reliable. A good mentor is also an active listener and a motivator.[9] The best mentors commit to being accessible and come to the relationship sincerely wanting to offer help in the mentee's best interest.[12]

One good practice is to provide mentors with a checklist of questions to ask their mentees. These questions should not just cover academic achievement expectations, but also solicit information on how the mentee feels about their professional work and their overall well-being. This can create a framework for meetings, starting conversations, and allowing exploration of concerns beyond the mentee's career goals.[6]

Characteristics of Good Mentees

Conversely, good mentees also demonstrate certain desirable characteristics. First, they demonstrate the willingness to fully participate in self-evaluation and developing an awareness of their own strengths and weaknesses. For example, our mentoring program requires all junior faculty (assistant professors) to complete an individual development program (IDP), which is a modified version of one we created for PhD research scientists.[13]

An IDP articulates faculty long- and short-term goals. It ensures that prior to meeting with their mentors, faculty have considered their trajectory, defined their perceived strengths and weaknesses, and begun to consider additional tools they might need to move toward their academic goals. An IDP doesn't have to be perfect from the outset, but it can set the stage for conversations about the mentee's career direction. We ask junior faculty to revisit their IDP annually to assess their progress and perhaps consider changing their goals and developing new strengths.

A good mentee should also be willing to initiate mentor conversations and connections. Sometimes described as "managing up," proactively working to guide these relationships by asking questions and requesting and listening to feedback are additional marks of good mentees.[14] They will also follow up with mentor recommendations and be thoughtful and appreciative of the mentor's time.

Features of Successful Mentorships

Beyond the characteristics that make for "good" mentors and mentees, there are features of the relationship itself that can portend mentoring success. Indeed, several key themes emerge from our conversations with mentees who enjoy strong mentorships. These include:

- **Alignment of values and goals with the mentee's best interests in mind.** This is an important component to ensure there is no sense of competition or mentor power over the mentee's career direction.

- **Shared understanding of goals.** From the outset the goals of mentoring should be set and agreed upon by the mentor and mentee in writing. While somewhat symbolic, such a "contract" outlines the confidential relationship, formalizes each party's commitment to the task, and clearly defines expectations. This offers a framework around which both mentor and mentee can establish a mutually beneficial partnership. It also helps to establish a timeline for formal "sit down" discussions and to connect on an as-needed basis. It is important to review together an updated CV several times a year.
- **Respectful separation**. The ability of either party to decline a pairing because of a mismatch as a "no-fault separation" is critical. This should be managed by a department mentoring director. While separations are uncommon in our experience, this option minimizes the creation of unsuccessful or detrimental partnerships. We strive to limit any consequences of mentoring changes through confidential discussions with both parties.

Mentoring Benefits Everyone

Good mentorships do not just happen. Experienced mentors will have learned from prior relationships, but inexperienced faculty will benefit from guidance around how to do this important job---mentoring the mentors, if you will. Indeed, offering workshops on mentoring is an important aspect of a successful program.

Personal connection is a key feature of the most successful mentoring relationships and is sometime best forged outside the reading room and office. Some of the strongest relationships can develop through out-of-hours shared meals and activities. But ultimately, it is commitment and the generous sharing of ideas and time that determine a mentorship's success. When both mentor and mentee see---and realize---the benefits, a department's investment in mentorship benefits everyone.

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Fast 5 at RSNA ’22: Looking into Radiology’s Crystal Ball

Kerri Reeves

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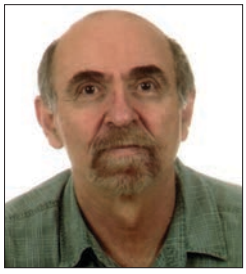


Donald L Resnick, MD, professor emeritus in the department of radiology at the University of California, San Diego, kicked off the RSNA Fast 5 with “Of Skeletons, Scholars and Sleuths: A Look Back, a Look Around and a Quick Look Ahead.”

“It is always wise to look ahead,” Donald L Resnick, MD, said, quoting Winston Churchill, “but difficult to look further than you can see.”

Nevertheless, Dr Resnick, professor emeritus of radiology at the University of California, San Diego, along with almost a dozen of his colleagues took a cautious attempt at clairvoyancy in the 2022 edition of the “Fast 5” at December’s Radiological Society of North America (RSNA) Scientific Assembly and Annual Meeting in Chicago.

In brief TED talk-style presentations on topics ranging from climate change, artificial intelligence (AI) and telemedicine, to the COVID-19 pandemic and emergence of corporate medicine, the radiologists shared their predictions of how these developments could change medical imaging technology and practice during the next five years.

Looking Behind to Gain Perspective on What’s Ahead

Dr Resnick spoke about how dramatically radiology has evolved over decades, portending a potential rebranding of the field. He recalled how his late father, Benjamin, in the early 1960s developed films in the darkroom, analyzed the images on a single view box, typed up his report and then handed it to the younger Dr Resnick to hand deliver to the referring physician.

Could his father ever have foreseen the field’s evolution from basic radiography to ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), mammography, positron emission tomography (PET), and molecular imaging? Dr Resnick asked rhetorically. Obviously not, he concluded and proceeded to predict the terms “radiology” and “radiologist” eventually will be replaced.

“Radiology is the science of dealing with X-rays and other high-energy radiation, but we also deal with ultrasonography, MRI, and many other techniques. We’re medical imagers and interventionalists, no longer just radiologists,” he said, adding that AI holds great promise for the field. But he cautioned his peers to apply the technology wisely and to ensure the technology works alongside them, not in place of them.

Radiologists as “Masters of Medicine”

Will radiology survive? It’s a question that’s been asked in one way or another during the past several years as the healthcare field overall struggles with burnout and workforce shortages. Of course it will survive, said William B Morrison, MD, FACR, professor of radiology and director of the division of general and musculoskeletal radiology at Thomas Jefferson University in Philadelphia.

“We’re on the cusp of major change in medicine,” argued Dr Morrison, who went on in his presentation to propose that, “after the next decade, [radiologists] could be the ‘masters of medicine’ if we play our cards right.”

Given the expansion of telemedicine, the growth of radiologic consultation, and the emergence of new and improved diagnostic modalities—such as hybrid PET-MRI, photon-counting CT, new nuclear

medicine radiotracers, and theranostics—as well as minimally invasive imaging-guided procedures and implementation of AI, Dr Morrison predicted the role of radiologists eventually will go beyond simply supplying and interpreting the images.

"We need to be on the front lines, guiding primary care physicians regarding what imaging exams to order, and then following through with them. We can also suggest imaging-guided, minimally invasive treatments for their patients in early stages of disease," said Dr Morrison, who also foresees greater radiologist direct interaction with patients, especially via telehealth, to provide support and education.

"Radiologists have a wide knowledge base and a 10,000-foot view of health care. If we leverage our talent and position, we can be involved in all stages of patient care," he said. "This impact and empowerment will neutralize burnout; we will be doing a variety of important jobs without the explosion of unnecessary exams we currently face."

Dr Morrison added that professional organizations must commit to investing in and demonstrating radiology's value to patients and payers, including through developing and testing AI applications and innovating new diagnostic and therapeutic tools.

"We need to retrain ourselves and train residents differently to optimize our value in the new medical environment," he concluded.

Making Friends with Teleradiology

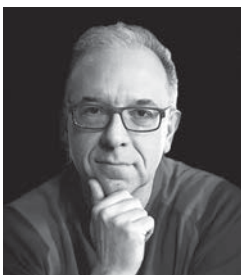
Bethany U Casagranda, DO, chair of the department of radiology and imaging institute for Allegheny Health Network in Pittsburgh, Pennsylvania, shared her thoughts on teleradiology as a "friend or foe" of academic radiology.

"We historically have raised concerns in our academic practices because [we] value items that can be lost in teleradiology," Dr Casagranda said, pointing to in-person education, professional relationships, and side conversations with colleagues that can inspire research and other scholarly activity.

Twenty years ago, Dr Casagranda said, she viewed teleradiology as a foe that threatened such human-centered, foundational functions of academic radiology.

"You did [everything] all together, and teleradiology threatened that togetherness," she said. "'You're breaking up the family,' and you don't want to break up the family."

But today, Dr Casagranda said, she considers teleradiology a "friend" of academic radiology. As



William B Morrison, MD, FACR, professor of radiology and director of the division of general and musculoskeletal radiology at Thomas Jefferson University in Philadelphia, AKA "Optimist Prime," says we are entering a "Renaissance period" in radiology.

Reed A Omary, MD, MS, Carol D and Henry P Pendergrass Professor and chair of the department of radiology at Vanderbilt University Medical Center in Nashville, Tennessee, presented on ecoradiology at RSNA.

Mark E Schweitzer, MD, vice president of health affairs at Wayne State University, Detroit, voiced concerns about the corporate practice of medicine in a Fast 5 presentation at RSNA 2022.

a radiologist working in a system with 10 hospitals and 28 outpatient imaging centers that generated over 1 million work RVUs in subspecialty reads in 2022, Dr Casagranda said such large volumes of studies can no longer be performed over such large regions under the "old-fashioned way" of doing radiology.

"In recent times, ignited by the pandemic, there's been a seismic shift in how we do work," she said, citing challenges such as after-hours and multispecialty interpretation amid increased case complexity, growing expectations of faster turnaround times, and meeting the needs of the underserved through teleradiology.

She expressed her view that academic radiology and teleradiology can coexist without a "tug of war on control" by engaging junior staff early, meeting the changing expectations and demands of an evolving workforce, and prioritizing inclusivity to attract the best and brightest minds to radiology.

A Shorter Work Week?

One of the defining expectations of the next generation of radiology employees is flexibility—a trend that was accelerated by the pandemic. In some cases, this may mean being able to work from home; in others it may mean a work week that of 32 or even just 30 hours, said Timothy J Mosher, MD. Dr Mosher is a physician advisor for the Center of Excellence for Improving Diagnosis and the Kenneth L Miller Chair of the department of radiology and distinguished professor of radiology and orthopedic surgery at Penn State University. Mosher predicted flexibility will become the watchword of full-time employment across many industries, including health care.

"You're not going to have a choice. This will not be an internal disruptor but an external one that comes from the bottom up … . A huge change [is coming] in the demographics and availability of the workforce. [They are] expecting different things in their work/life balance," said Dr Mosher, noting that many companies outside health care have already switched to a 30-hour week.

"The future is a lot closer than it would appear," he said.

The Advent of Green Radiology

Reed A Omary, MD, MS meanwhile, had a similar take on the future of radiology with respect to environmental issues. The Carol D and Henry P Pendergrass Professor, chair of the radiology and radiological science department, and a professor of biomedical engineering at Vanderbilt University Medical Center and School of Medicine in Nashville, Tennessee, addressed the imminent dangers of climate change and radiology's role in both contributing to and helping alleviate those dangers.

"As climate change disproportionately amplifies existing social and health inequities, ecoradiology fits squarely into health care's current diversity, equity, and inclusion initiatives," Dr Omary said, explaining that climate change, which the World Health Organization cites as the biggest health threat facing humanity, puts annual direct costs of over $2 billion on health care.

"Outside of health care, these issues are clumped together into what is termed 'ESG,' or environmental, social, and governance reporting. In coming years, I predict we will see ESG reporting of our outcomes in a similar way," he said, adding that the health care industry is a major contributor to greenhouse gases.

Predicting that more than 100 papers will be published by radiology experts in 2024 on environmental sustainability and climate change, Dr Omary urged his audience to help combat climate change by establishing "green teams" in their departments to develop programs to reduce their environmental footprint and foster a culture of sustainability.

He also recommended evaluating vendors based not solely on prices, but on the environmental impact of supplies, and selecting vendors who, for example, reduce the amount of plastic in their packaging or design imaging devices with replaceable and/or modular components.

Preparing for "Corporate Medicine"

The corporate practice of medicine doctrine, which originated near the turn of the 20th century, prohibits corporations from practicing medicine or employing physicians to provide professional medical services. The doctrine does not, however, ban the business administration of medicine; these include such functions as billing and operations.

But what was once meant to protect physicians will become a major threat to radiologists over the next several years, says Mark E Schweitzer, MD, vice president of health affairs at Wayne State University in Detroit, Michigan.

"Corporations have intrinsic advantages over physicians when practicing medicine. They have access to capital, efficiencies of scale, vendor informatics staffing, and statuary legal protection. Radiology groups have none of those advantages," Dr Schweitzer said, detailing various microeconomic biases that hurt individual physicians.

Among them:

- **Rent-seeking**: Rules and regulations that are designed to benefit one group over another (corporations over individual physicians);
- **The Matthew Effect:** The rich will always get richer as corporations push the envelope in terms of billing, find workarounds for rules, and lobby successfully for additional rent-seeking opportunities; and
- **Negative externalities**: The occurrence of a "product" exerting a negative effect on a third-party independent.

"I can run a corporation and say that the radiologists have to read 200 films an hour. That radiologist who [misses a lesion] can be sued for malpractice, but me as the overlord, I can't be sued for malpractice," he explained. ""[These] economic effects are well known and biased against individual physicians and practices."

The percentage of acute-care hospitals with corporate investments has steadily risen from 6.3% in 1975, to 9.9% in 1981, to 49.1% in 2010 and skyrocketing to 59.9% in 2015. As a result, more physicians are now employed by corporations than are self-employed or employed by small private practices.

This, Dr Schweitzer said, could lead to scenarios in which the corporation's obligations to shareholders do not align with the physician's judgements and obligations to patients.

"I think there will be more and more radiologists employed by publicly traded and privately-owned corporations," Dr Schweitzer predicted, advising radiologists to gain an understanding of the legal and statutory advantages of corporate health care systems.

"It's also beneficial to become your own leader, so that even if you work for a corporation, physicians and radiologists are placed in positions of leadership," Dr Schweitzer added.

Radiology Education, Sports, Radiomics

In other Fast 5 presentations, experts predicted that over the next half-decade:

- Radiology training will be driven by AI and tailored to each resident's own strengths and weaknesses.
- Return-to-play decisions for players at all levels of athletics will increasingly be guided by radiologists using advanced imaging techniques such as quantitative imaging, T2 mapping, and elastography.
- Radiomics will become routine, going beyond applications in cancer to playing a role in imaging Alzheimer disease, cardiac conditions, pancreatitis, kidney stones, and musculoskeletal conditions. Together with proteomics, genomics, and metabolomics, clinicians will create increasingly accurate models of health and disease to advance precision health care.

It's Only the Beginning

The takeaway message from all the Fast 5 presentations amounted to an overall belief in the power and ability of radiology and its practitioners to embrace change and play a greater role in the practice of medicine over the next decade.

"We can take the reins of medicine," Dr Morrison said. "The majority of diagnoses are made through imaging. We're at the forefront of AI development, and we have new diagnostic and therapeutic tools at our fingertips."

Magnetic Resonance Imaging (MRI) can be an Important Diagnostic Tool for Breast Cancer Detection in Patients with Dense Breast

The American Society of Breast Surgeons recommends considering supplemental imaging (breast MRI or ultrasound) in addition to annual mammography in women with increased breast density (C and D density)* (beginning at age 40)[1]

* Class C or 3 density = heterogeneously dense; Class D or 4 density = extremely dense

Indication

Gadavist® (gadobutrol) injection is a gadolinium-based contrast agent indicated for use with magnetic resonance imaging (MRI) to assess the presence and extent of malignant breast disease in adult patients.

Important Safety Information

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.

- The risk of NSF appears highest among patients with:
  - Chronic, severe kidney disease (GFR <30 mL/min/1.73m^2), or
  - Acute kidney injury
- Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (for example, age >60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.
- For patients at highest risk for NSF, do not exceed the recommended GADAVIST dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration.

Contraindication and Important Information about Hypersensitivity Reactions: Gadavist® is contraindicated in patients with history of severe hypersensitivity reactions to Gadavist®. Anaphylactic and other hypersensitivity reactions with cardiovascular, respiratory, or cutaneous manifestations, ranging from mild to severe, including death, have uncommonly occurred following Gadavist® administration. Before Gadavist® administration, assess all patients for any history of a reaction to contrast media, bronchial asthma and/or allergic disorders. These patients may have an increased risk for a hypersensitivity reaction to Gadavist®.

Gadolinium Retention: Gadolinium is retained for months or years in several organs. Linear GBCAs cause more retention than macrocyclic GBCAs. At equivalent doses, retention varies among the linear agents. Retention is lowest and similar among the macrocyclic GBCAs. Consequences of gadolinium retention in the brain have not been established, but they have been established in the skin and other organs in patients with impaired renal function. While clinical consequences of gadolinium retention have not been established in patients with normal renal function, certain patients might be at higher risk. These include patients requiring multiple lifetime doses, pregnant and pediatric patients, and patients with inflammatory conditions. Consider the retention characteristics of the agent and minimize repetitive GBCA studies, when possible.

Please see brief summary on adjacent pages.

Gadavist® (gadobutrol) Injection Is the First and Only Gadolinium-based Contrast Agent Approved for Breast MRI

Visit Gadavist.com or schedule time with a Bayer in Radiology representative to learn more

Important Safety Information (continued)

Acute Kidney Injury: In patients with chronic renal impairment, acute kidney injury sometimes requiring dialysis has been observed with the use of GBCAs. Do not exceed the recommended dose; the risk of acute kidney injury may increase with higher than recommended doses.

Extravasation and Injection Site Reactions: Ensure catheter and venous patency before the injection of Gadavist®. Extravasation into tissues during Gadavist® administration may result in moderate irritation.

Overestimation of Extent of Malignant Disease in MRI of the Breast: Gadavist® MRI of the breast overestimated the histologically confirmed extent of malignancy in the diseased breast in up to 50% of the patients.

Adverse Reactions: The most frequent (≥0.5%) adverse reactions associated with Gadavist® in clinical studies were headache (1.7%), nausea (1.2%) and dizziness (0.5%).

Please see brief summary on adjacent pages.

Reference: 1. Consensus Statement on Screening Mammography. The American Society of Breast Surgeons website. https://www.breastsurgeons.org/docs/statements/Position-Statement-on-Screening-Mammography.pdf. Accessed June 9, 2020.

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1 mmol/mL

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GADAVIST (gadobutrol) injection, for intravenous use
Initial U.S. Approval: 2011

BRIEF SUMMARY OF PRESCRIBING INFORMATION
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WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.

- **The risk for NSF appears highest among patients with:**
  - **Chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2), or**
  - **Acute kidney injury.**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (for example, age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.**
- **For patients at highest risk for NSF, do not exceed the recommended Gadavist dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration *[see Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

1.1 Magnetic Resonance Imaging (MRI) of the Central Nervous System (CNS)

Gadavist is indicated for use with magnetic resonance imaging (MRI) in adult and pediatric patients, including term neonates, to detect and visualize areas with disrupted blood brain barrier and/or abnormal vascularity of the central nervous system.

1.2 MRI of the Breast

Gadavist is indicated for use with MRI in adult patients to assess the presence and extent of malignant breast disease.

1.3 Magnetic Resonance Angiography (MRA)

Gadavist is indicated for use in magnetic resonance angiography (MRA) in adult and pediatric patients, including term neonates, to evaluate known or suspected supra-aortic or renal artery disease.

1.4 Cardiac MRI

Gadavist is indicated for use in cardiac MRI (CMRI) to assess myocardial perfusion (stress, rest) and late gadolinium enhancement in adult patients with known or suspected coronary artery disease (CAD).

4 CONTRAINDICATIONS

Gadavist is contraindicated in patients with history of severe hypersensitivity reactions to Gadavist.

5 WARNINGS AND PRECAUTIONS

5.1 Nephrogenic Systemic Fibrosis

Gadolinium-based contrast agents (GBCAs) increase the risk for nephrogenic systemic fibrosis (NSF) among patients with impaired elimination of the drugs. Avoid use of GBCAs among these patients unless the diagnostic information is essential and not available with non-contrast MRI or other modalities. The GBCA-associated NSF risk appears highest for patients with chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2) as well as patients with acute kidney injury. The risk appears lower for patients with chronic, moderate kidney disease (GFR 30 to 59 mL/min/1.73m^2) and little, if any, for patients with chronic, mild kidney disease (GFR 60 to 89 mL/min/1.73m^2). NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs. Report any diagnosis of NSF following Gadavist administration to Bayer Healthcare (1-888-842-2937) or FDA (1-800-FDA-1088 or www.fda.gov/medwatch).

Screen patients for acute kidney injury and other conditions that may reduce renal function. Features of acute kidney injury consist of rapid (over hours to days) and usually reversible decrease in kidney function, commonly in the setting of surgery, severe infection, injury or drug-induced kidney toxicity. Serum creatinine levels and estimated GFR may not reliably assess renal function in the setting of acute kidney injury. For patients at risk for chronically reduced renal function (for example, age > 60 years, diabetes mellitus or chronic hypertension), estimate the GFR through laboratory testing.

Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA and degree of renal impairment at the time of exposure. Record the specific GBCA and the dose administered to a patient. For patients at highest risk for NSF, do not exceed the recommended Gadavist dose and allow a sufficient period of time for elimination of the drug prior to re-administration. For patients receiving hemodialysis, consider the prompt initiation of hemodialysis following the administration of a GBCA in order to enhance the contrast agent's elimination *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*. The usefulness of hemodialysis in the prevention of NSF is unknown *[see Clinical Pharmacology (12.3)]*.

5.2 Hypersensitivity Reactions

Anaphylactic and other hypersensitivity reactions with cardiovascular, respiratory or cutaneous manifestations, ranging from mild to severe, including death, have uncommonly occurred following Gadavist administration *[see Adverse Reactions (6)]*.

- Before Gadavist administration, assess all patients for any history of a reaction to contrast media, bronchial asthma and/or allergic disorders. These patients may have an increased risk for a hypersensitivity reaction to Gadavist.
- Administer Gadavist only in situations where trained personnel and therapies are promptly available for the treatment of hypersensitivity reactions, including personnel trained in resuscitation.

Most hypersensitivity reactions to Gadavist have occurred within half an hour after administration. Delayed reactions can occur up to several days after administration. Observe patients for signs and symptoms of hypersensitivity reactions during and following Gadavist administration.

5.3 Gadolinium Retention

Gadolinium is retained for months or years in several organs. The highest concentrations (nanomoles per gram of tissue) have been identified in the bone, followed by other organs (for example, brain, skin, kidney, liver, and spleen). The duration of retention also varies by tissue and is longest in bone. Linear GBCAs cause more retention than macrocyclic GBCAs. At equivalent doses, gadolinium retention varies among the linear agents with Omniscan (gadodiamide) and Optimark (gadoversetamide) causing greater retention than other linear agents [Eovist (gadoxetate disodium), Magnevist (gadopentetate dimeglumine), MultiHance (gadobenate dimeglumine)]. Retention is lowest and similar among the macrocyclic GBCAs [Dotarem (gadoterate meglumine), Gadavist (gadobutrol), ProHance (gadoteridol)].

Consequences of gadolinium retention in the brain have not been established. Pathologic and clinical consequences of GBCA administration and retention in skin and other organs have been established in patients with impaired renal function *[see Warnings and Precautions (5.1)]*. There are rare reports of pathologic skin changes in patients with normal renal function. Adverse events involving multiple organ systems have been reported in patients with normal renal function without an established causal link to gadolinium retention *[see Adverse Reactions (6.2)]*.

While clinical consequences of gadolinium retention have not been established in patients with normal renal function, certain patients might be at higher risk. These include patients requiring multiple lifetime doses, pregnant and pediatric patients, and patients with inflammatory conditions. Consider the retention characteristics of the agent when choosing a GBCA for these patients. Minimize repetitive GBCA imaging studies particularly closely spaced studies, when possible.

5.4 Acute Kidney Injury

In patients with chronic renal impairment, acute kidney injury sometimes requiring dialysis has been observed with the use of some GBCAs. Do not exceed the recommended dose; the risk of acute kidney injury may increase with higher than recommended doses.

5.5 Extravasation and Injection Site Reactions

Ensure catheter and venous patency before the injection of Gadavist. Extravasation into tissues during Gadavist administration may result in moderate irritation *[see Nonclinical Toxicology (13.2)]*.

5.6 Overestimation of Extent of Malignant Disease in MRI of the Breast

Gadavist MRI of the breast overestimated the histologically confirmed extent of malignancy in the diseased breast in up to 50% of the patients *[see Clinical Studies (14.2)]*.

5.7 Low Sensitivity for Significant Arterial Stenosis

The performance of Gadavist MRA for detecting arterial segments with significant stenosis (>50% renal, >70% supra-aortic) has not been shown to exceed 55%. Therefore, a negative MRA study alone should not be used to rule out significant stenosis *[see Clinical Studies (14.3)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in labeling:

- Nephrogenic Systemic Fibrosis (NSF) *[see Boxed Warning and Warnings and Precautions (5.1)]*.
- Hypersensitivity reactions *[see Contraindications (4) and Warnings and Precautions (5.2)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The adverse reactions described in this section reflect Gadavist exposure in 7,713 subjects (including 184 pediatric patients, ages 0 to 17 years) with the majority receiving the recommended dose. Approximately 52% of the subjects were male and the ethnic distribution was 62% Caucasian, 28% Asian, 5%

Hispanic, 2.5% Black, and 2.5% patients of other ethnic groups. The average age was 56 years (range from 1 week to 93 years).

Overall, approximately 4% of subjects reported one or more adverse reactions during a follow-up period that ranged from 24 hours to 7 days after Gadavist administration.

Adverse reactions associated with the use of Gadavist were usually mild to moderate in severity and transient in nature.

Table 2 lists adverse reactions that occurred in ≥ 0.1% subjects who received Gadavist.

Table 2: Adverse Reactions

Reaction	Rate (%) n=7713
Headache	1.7
Nausea	1.2
Dizziness	0.5
Dysgeusia	0.4
Feeling Hot	0.4
Injection site reactions	0.4
Vomiting	0.4
Rash (includes generalized, macular, papular, pruritic)	0.3
Erythema	0.2
Paresthesia	0.2
Pruritus (includes generalized)	0.2
Dyspnea	0.1
Urticaria	0.1

Adverse reactions that occurred with a frequency of < 0.1% in subjects who received Gadavist include: hypersensitivity/anaphylactic reaction, loss of consciousness, convulsion, parosmia, tachycardia, palpitation, dry mouth, malaise and feeling cold.

6.2 Postmarketing Experience

The following additional adverse reactions have been reported during postmarketing use of Gadavist. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Cardiac arrest
- Nephrogenic Systemic Fibrosis (NSF)
- Hypersensitivity reactions (anaphylactic shock, circulatory collapse, respiratory arrest, pulmonary edema, bronchospasm, cyanosis, oropharyngeal swelling, laryngeal edema, blood pressure increased, chest pain, angioedema, conjunctivitis, hyperhidrosis, cough, sneezing, burning sensation, and pallor) *[see Warnings and Precautions (5.2)]*.
- General Disorders and Administration Site Conditions: Adverse events with variable onset and duration have been reported after GBCA administration *[see Warnings and Precautions (5.3)]*. These include fatigue, asthenia, pain syndromes, and heterogeneous clusters of symptoms in the neurological, cutaneous, and musculoskeletal systems.
- Skin: Gadolinium associated plaques

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

GBCAs cross the placenta and result in fetal exposure and gadolinium retention. The human data on the association between GBCAs and adverse fetal outcomes are limited and inconclusive *(see Data)*. In animal reproduction studies, although teratogenicity was not observed, embryolethality was observed in monkeys, rabbits and rats receiving intravenous gadobutrol during organogenesis at doses 8 times and above the recommended human dose. Retardation of embryonal development was observed in rabbits and rats receiving intravenous gadobutrol during organogenesis at doses 8 and 12 times, respectively, the recommended human dose *(see Data)*. Because of the potential risks of gadolinium to the fetus, use Gadavist only if imaging is essential during pregnancy and cannot be delayed.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and is 15 to 20%, respectively.

Data

Human Data.

Contrast enhancement is visualized in the placenta and fetal tissues after maternal GBCA administration.

Cohort studies and case reports on exposure to GBCAs during pregnancy have not reported a clear association between GBCAs and adverse effects in the exposed neonates. However, a retrospective cohort study, comparing pregnant women who had a GBCA MRI to pregnant women who did not have an MRI, reported a higher occurrence of stillbirths and neonatal deaths in the group receiving GBCA MRI. Limitations of this study include a lack of comparison with non-contrast MRI and lack of information about the maternal indication for MRI. Overall, these data preclude a reliable evaluation of the potential risk of adverse fetal outcomes with the use of GBCAs in pregnancy.

Animal Data

Gadolinium Retention

GBCAs administered to pregnant non-human primates (0.1 mmol/kg on gestational days 85 and 135) result in measurable gadolinium concentration in the offspring in bone, brain, skin, liver, kidney, and spleen for at least 7 months. GBCAs administered to pregnant mice (2 mmol/kg daily on gestational days 16 through 19) result in measurable gadolinium concentrations in the pups in bone, brain, kidney, liver, blood, muscle, and spleen at one month postnatal age.

Reproductive Toxicology

Embryolethality was observed when gadobutrol was administered intravenously to monkeys during organogenesis at doses 8 times the recommended single human dose (based on body surface area); gadobutrol was not maternally toxic or teratogenic at this dose. Embryolethality and retardation of embryonal development also occurred in pregnant rats receiving maternally toxic doses of gadobutrol (≥ 7.5 mmol/kg body weight; equivalent to 12 times the human dose based on body surface area) and in pregnant rabbits (≥ 2.5 mmol/kg body weight; equivalent to 8 times the recommended human dose based on body surface area). In rabbits, this finding occurred without evidence of pronounced maternal toxicity and with minimal placental transfer (0.01% of the administered dose detected in the fetuses).

Because pregnant animals received repeated daily doses of Gadavist, their overall exposure was significantly higher than that achieved with the standard single dose administered to humans.

8.2 Lactation

Risk Summary

There are no data on the presence of gadobutrol in human milk, the effects on the breastfed infant, or the effects on milk production. However, published lactation data on other GBCAs indicate that 0.01 to 0.04% of the maternal gadolinium dose is present in breast milk and there is limited GBCA gastrointestinal absorption in the breast-fed infant. Gadobutrol is present in rat milk *(see Data)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Gadavist and any potential adverse effects on the breastfed infant from Gadavist or from the underlying maternal condition.

Data

In lactating rats receiving 0.5 mmol/kg of intravenous [^{153}Gd]-gadobutrol, 0.01% of the total administered radioactivity was transferred to the pup via maternal milk within 3 hours after administration, and the gastrointestinal absorption is poor (approximately 5% of the dose orally administered was excreted in the urine).

8.4 Pediatric Use

The safety and effectiveness of Gadavist have been established in pediatric patients, including term neonates, for use with MRI to detect and visualize areas with disrupted blood brain barrier and/or abnormal vascularity of the central nervous system and for use in MRA to evaluate known or suspected supra-aortic or renal artery disease. Use of Gadavist in these indications is supported by adequate and well-controlled studies in adults and supportive imaging data in two studies in 135 patients 2 to less than 18 years of age and 44 patients less than 2 years of age with CNS and non-CNS lesions, and pharmacokinetic data in 130 patients 2 to less than 18 years of age and 43 patients less than 2 years of age, including term neonates *[see Clinical Pharmacology (12.3) and Clinical Studies (14.1)]*. The frequency, type, and severity of adverse reactions in pediatric patients were similar to adverse reactions in adults *[see Adverse Reactions (6.1)]*. No dose adjustment according to age is necessary in pediatric patients *[see Dosage and Administration (2.1), Clinical Pharmacology (12.3), and Clinical Studies (14.1)]*. The safety and effectiveness of Gadavist have not been established in preterm neonates for any indication or in pediatric patients of any age for use with MRI to assess the presence and extent of malignant breast disease, or for use in CMRI to assess myocardial perfusion (stress, rest) and late gadolinium enhancement in patients with known or suspected coronary artery disease (CAD).

NSF Risk

No case of NSF associated with Gadavist or any other GBCA has been identified in pediatric patients ages 6 years and younger. Pharmacokinetic studies suggest that clearance of Gadavist is similar in pediatric patients and adults, including pediatric patients age younger than 2 years. No increased risk factor for NSF has been identified in juvenile animal studies of gadobutrol. Normal estimated GFR (eGFR) is around 30 mL/min/1.73m^2 at birth and increases to mature levels around 1 year of age, reflecting growth in both glomerular function and relative body surface area. Clinical studies in pediatric patients younger than 1 year of age have been conducted in patients with the following

minimum eGFR: 31 mL/min/1.73m^2 (age 2 to 7 days), 38 mL/min/1.73m^2 (age 8 to 28 days), 62 mL/min/1.73m^2 (age 1 to 6 months), and 83 mL/min/1.73m^2 (age 6 to 12 months).

Juvenile Animal Data

Single and repeat-dose toxicity studies in neonatal and juvenile rats did not reveal findings suggestive of a specific risk for use in pediatric patients including term neonates and infants.

8.5 Geriatric Use

In clinical studies of Gadavist, 1,377 patients were 65 years of age and over, while 104 patients were 80 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, use of Gadavist in elderly patients should be cautious, reflecting the greater frequency of impaired renal function and concomitant disease or other drug therapy. No dose adjustment according to age is necessary in this population.

8.6 Renal Impairment

Prior to administration of Gadavist, screen all patients for renal dysfunction by obtaining a history and/or laboratory tests *[see Warnings and Precautions (5.1)]*. No dosage adjustment is recommended for patients with renal impairment.

Gadavist can be removed from the body by hemodialysis *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

The maximum dose of Gadavist tested in healthy volunteers, 1.5 mL/kg body weight (1.5 mmol/kg; 15 times the recommended dose), was tolerated in a manner similar to lower doses. Gadavist can be removed by hemodialysis *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies of gadobutrol have been conducted.

Gadobutrol was not mutagenic in *in vitro* reverse mutation tests in bacteria, in the HGPRT (hypoxanthine-guanine phosphoribosyl transferase) test using cultured Chinese hamster V79 cells, or in chromosome aberration tests in human peripheral blood lymphocytes, and was negative in an *in vivo* micronucleus test in mice after intravenous injection of 0.5 mmol/kg.

Gadobutrol had no effect on fertility and general reproductive performance of male and female rats when given in doses 12.2 times the human equivalent dose (based on body surface area).

13.2 Animal Toxicology and/or Pharmacology

Local intolerance reactions, including moderate irritation associated with infiltration of inflammatory cells was observed after paravenous administration to rabbits, suggesting the possibility of occurrence of local irritation if the contrast medium leaks around veins in a clinical setting *[see Warnings and Precautions (5.5)]*.

17 PATIENT COUNSELING INFORMATION

- Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Nephrogenic Systemic Fibrosis

Instruct patients to inform their physician if they:

- Have a history of kidney disease and/or liver disease, or
- Have recently received a GBCA

GBCAs increase the risk of NSF among patients with impaired elimination of drugs. To counsel patients at risk of NSF:

- Describe the clinical manifestation of NSF
- Describe procedures to screen for the detection of renal impairment

Instruct the patients to contact their physician if they develop signs or symptoms of NSF following Gadavist administration, such as burning, itching, swelling, scaling, hardening and tightening of the skin; red or dark patches on the skin; stiffness in joints with trouble moving, bending or straightening the arms, hands, legs or feet; pain in the hip bones or ribs; or muscle weakness.

Common Adverse Reactions

Inform patients that they may experience:

- Reactions along the venous injection site, such as mild and transient burning or pain or feeling of warmth or coldness at the injection site
- Side effects of headache, nausea, abnormal taste and feeling hot

General Precautions

Gadolinium Retention

- Advise patients that gadolinium is retained for months or years in brain, bone, skin, and other organs in patients with normal renal function. The clinical consequences of retention are unknown. Retention depends on multiple factors and is greater following administration of linear GBCAs than following administration of macrocyclic GBCAs. *[see Warnings and Precautions (5.3)]*.

Instruct patients receiving Gadavist to inform their physician if they:

- Are pregnant or breastfeeding
- Have a history of allergic reaction to contrast media, bronchial asthma or allergic respiratory disorder

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Working at the Intersection of Radiology and Global Health Equity

Monica M Matsumoto, MD; and Farouk Dako, MD

Equitable access to medical imaging is an essential component of health care. The World Health Organization and United Nations prioritize health and well-being as one of their Sustainable Development Goals, with medical imaging occupying a universally important role in the provision of medical care.[1,2] For example, healthcare workers in high-income countries (HICs) are increasingly relying on medical imaging, whether in triaging trauma patients, evaluating for infection, managing oncologic treatment, or performing image-guided interventions. [3,4] However, enormous disparities exist in access to medical imaging in low- and middle-income countries (LMICs).[5] Broadly, "global health" refers to fields that aim to address health problems across the world, traditionally relying on partnerships between high- and low-resource settings.[4] Radiology, as a central component in managing care, is not only well positioned but also obligated to participate in global health outreach. This review discusses opportunities for radiology to reduce care disparities across the world, specifically in expanding access to basic and advanced medical imaging, contributing to human capacity building and mitigation of brain drain, and incorporating principles of medical ethics and research into collaborations.

Access to Medical Imaging

A huge proportion of the global population continues to lack access to radiology services.[4] For example, computed tomography (CT) scanners are ubiquitous in U.S. healthcare facilities, with 43 scanners per million inhabitants, compared to less than one scanner per million in LMICs.[3,6] An additional 11.4 CT scanners per million and 5.2 magnetic resonance imaging (MRI) scanners per million of population in LMICs are needed to reach similar levels of access as in HICs.[5] While many studies promote the use of radiography and ultrasound in LMICs, focusing exclusively on basic imaging modalities will perpetuate disparities between LMICs and HICs. While the utility of radiography and ultrasound is incontrovertible, advanced modalities such as CT, mammography, and MRI are critical to high-quality patient care and improved population health.[5] For example, Hricak, et al, used a microsimulation model to estimate that scaling up five diagnostic imaging modalities (ultrasound, X-ray, CT, MRI, and nuclear imaging) for cancer care would avert over 2.4 million deaths and save 33 million life years worldwide between 2020-2030 across all resource settings.[3] Scaling up imaging is necessary to realize survival gains and would provide a return of $179 per $1 invested.[3,7] Global health collaborations should plan for incremental incorporation of basic and advanced diagnostic modalities into patient care.

Changing demographics and epidemiology further underscore the need for imaging services. Premature death related to cancers is rising in LMICs, and this trend is expected to continue.[8] For example, lung cancer had the highest cancer-related mortality in 2020, with an expected shift in incidence and mortality to LMICs, owing to higher prevalence of smoking.[8] Low-dose chest CT for lung cancer screening in high-risk individuals has been shown to reduce lung cancer-related mortality.[8] Similarly, Konert, et al, demonstrated a benefit in progression-free and overall survival when newly incorporating positron emission tomography/CT into

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Radiology must be prepared globally to meet these demographic and epidemiological shifts, so that inequities are not further perpetuated and widened.

management algorithms of stage III non-small cell lung cancer in their cohort of primarily middle-income countries.[9] However, access to both CT and nuclear imaging remains limited, hampering population-wide benefits. Similarly, advanced imaging modalities are central to accessing minimally invasive interventions, including obtaining biopsies, managing postpartum hemorrhage, and treating postsurgical complications.[10] Radiology must be prepared globally to meet these demographic and epidemiological shifts, so that inequities are not further perpetuated and widened.

Human Capacity Building and Mitigation of Brain Drain

Ultimately, successful incorporation of medical imaging in LMICs requires a trained workforce, including technologists, radiologists, and medical physicists. The need for these professionals in LMICs is well documented.[5] For example, there are an estimated 25.9 medical doctors and 152.1 nursing/midwifery personnel per 10,000 people in North America compared to 2.3 and 12.6, respectively, in sub-Saharan Africa.[1] Furthermore, an additional 64.9 radiologists per million population must be trained in sub-Saharan LMICs to reach a level comparable to that of upper middle-income countries.[5] Observerships, short-term training courses, and virtual platforms are all educational avenues that have been utilized. [2,5] Training and capacity building are central tenets of health equity and are acute areas of need for more collaboration between HICs and LMICs.

Disparities in medical imaging are perpetuated by a lack of local training programs and infrastructure, as well as the phenomenon known as "brain drain". Brain drain is the migration of highly skilled and educated people from one country to another, especially from lower-resource to higher-resource environments.[11] Studies have shown increasing numbers of physician emigration from LMICs, and the US is one of the main beneficiaries of this trend, with a reported 60% of international medical graduates from LMICs.[11,12] The reasons for this migration of medical professionals are multifaceted and may include better training opportunities, local conflict or political instability, higher financial remuneration, and desire to practice at the highest level of their degrees.[11,12]

The result of emigration is persistent workforce shortage, resulting in persistent inequities that further incentivizes immigration. While brain drain can be partly attributed to local policies, resource allocation in LMICs, and merit-based immigration systems of HICs, it is also an ethical dilemma resulting from the inequitable transfer of human capital between regions. Global efforts are needed to build local capacity and promote business and industry partnerships for sustainable practices.[4,12] Building capacity in LMICs is a multifaceted endeavor that requires better training programs, improved infrastructure and working conditions, and advocacy to increase national health expenditure.

Global health initiatives should always seek to collaborate with a local champion, whether an individual or institution, in whom resources can be invested.[5,13] A focus on developing strong local affiliations and training programs can also help avoid many of the ethical dilemmas that can arise from medical service work. One example is the successful creation of an interventional radiology training program in Tanzania, built upon a combination of a strong local partner, recurrent short-term exchanges of healthcare professionals from HICs, and virtual programming.[14] Several other organizations and institutions support global health outreach and education, as well as the foundation of global health equity tracks in residency training programs, to address these disparities. These organizations include the Radiological Society of North America, American Society of Radiologic Technologists, and RAD-AID International, Furthermore, the rising interest in global health among radiology trainees is promising and should be supported as a component of training programs and job opportunities.[15]

Role of Ethics and Research in Health Equity

Global health outreach, no matter how well-intentioned the mission, will inevitably face ethical dilemmas and unintended consequences. An

in-depth description of medical ethics is beyond the scope of this article; however, several principles and frameworks should be followed to inform ethical decision making.[4,13] A classical, albeit Western-based, framework of medical ethics includes the principles of non-maleficence, beneficence, autonomy, and justice, although numerous other ethical principles, such as solidarity, privacy, equity, and transparency, can be included to promote culturally informed practices.[4,16].While a mere understanding of ethical principles does not ensure that best practices are upheld, these frameworks should serve as a foundation of global health partnerships.

Research is also a vital component of promoting global equity in radiology. For example, partnerships between researchers in HICs and LMICs are essential to understanding disease trends, developing treatment strategies, and addressing disparities in access to imaging services.[3,4] Parachute research, the act of extracting data from LMICs by individuals from HICs without proper acknowledgement, should be discouraged and replaced by engaging local stakeholder in all research projects, beginning with deciding research topics. Not all data from HICs can or should be extrapolated to LMICs, so research can help inform innovative, sustainable models for building high-quality imaging services in lower-resource settings, including incorporating artificial intelligence solutions.[3] One example is the PERTAIN trial, which specifically incorporated LMICs to assess the potential benefit of nuclear imaging in lung cancer treatment.[9] Moreover, research is a critical element of improving practice standards and supporting training, education, and professional development.[3] Ethical considerations and inclusive research collaborations are foundational tenets of building equity through global radiology.

Progress in global health imaging faces many challenges, including deficient imaging equipment, unequal access to radiology services, inadequate training, and insufficient data and standards. While these disparities contribute to worse health outcomes in LMICs, they also represent opportunities for change and engagement. Radiology has the dual mission of strengthening imaging services and human capacity building, a mission that should be informed by local collaboration and an understanding of medical ethics.

While not all of us in radiology may directly engage in efforts to improve global health, we have a collective responsibility to understand medical imaging's role in health equity, raise awareness of persistent disparities and ethical considerations, and support our colleagues who do participate in these efforts.

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From "Nice-to-Have" to "Must-Have:" AI's Inevitable Progression?

Amine Korchi, MD

Despite its enthusiastic acceptance by early adopters, artificial Intelligence (AI) has yet to reach the critical mass necessary to achieve the widespread utilization in radiology that one might expect for such a powerful technology.

Indeed, the AI chasm has not yet been crossed,[1,2] and it makes me wonder: Are AI-powered technologies destined to remain solely "nice-to-have" tools in our field, or do they have the potential to achieve "must-have" status?

I believe AI is headed toward the latter. Technology is at the core of radiology; X-ray machines, computed tomography (CT) and magnetic resonance imaging (MRI) scanners, and other imaging tools are just a few of the technologies that are essential to our work as radiologists.

Similarly, it is unthinkable nowadays to consider operating a radiology department without PACS, image viewers, and radiology information and speech recognition systems. Today's imaging data, workloads, and expected service and productivity are no longer those of 50 years ago. Without these technologies radiologists would simply not be able to run their practices and meet the demands of today's healthcare world.

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Indeed, they illustrate just how the evolution of medical needs over time have led to the development of solutions that were once considered nonessential but have now become must-have tools in radiology—and all of medical care, for that matter.

There is no reason to think AI will not follow a similar path. I remember a discussion I had with a colleague a few years ago. I told him that software had been created to detect bone fractures on plain X-rays with a level of accuracy close to that of radiologists.[3] He candidly replied that he did not need such software, as he was able to detect these injuries on his own. He suggested that such a tool would become, at most, a nice-to-have gimmick.

Since then, several AI-enabled tools are gradually providing imaging practices with growing levels of support. Even if AI software to support the detection of a fracture or a stroke continues to be perceived by many radiologists as a nice-to-have option, I believe that it can improve our overall performance, confidence, and experience.[4-7]

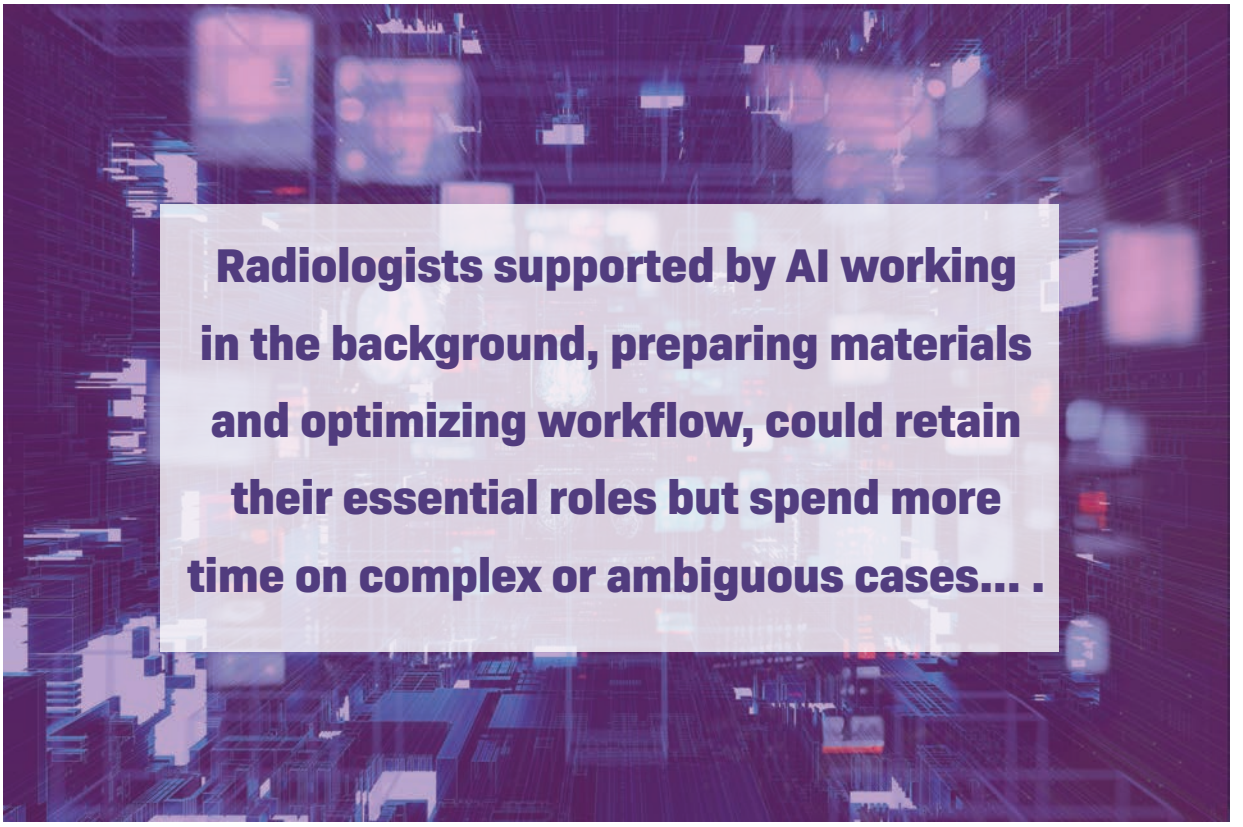
Artificial intelligence-powered software serves as a second pair of eyes, consistently and continuously working alongside us anytime and anywhere. It may help us avoid missing subtle abnormalities and can reinforce our confidence when determining exams are normal. It gives extra help during a long and strenuous day of work.

Obviously, AI has its shortcomings—it still generates its share of false-positives and false-negatives. But this does not discount its value when used reasonably with limitations in mind. Its benefits largely compensate for its use despite the limitations, and I believe its performance will undoubtedly improve with time.

In addition, AI has the ability to supercharge our equipment and quality can enable us to do more with less and improve our performance without compromising quality. For example, AI-based image reconstruction technology can significantly reduce image acquisition time, increase throughput, and reduce patient discomfort. [8,9] It is becoming increasingly clear that the next growth spurt in productivity and quality will be fueled by AI, strengthening its conversion from an accessory to an essential tool.

Consider, for example, AI has already started to gradually pervade our professional environment, and the more we integrate it, the more necessary it becomes.

AI-driven tools are currently mostly used to support radiologists in their visual interpretation-enabled automation of imaging findings. AI has the potential to do much more; it can facilitate the radiologists' daily workflow and become even more essential. Imagine a not-too-distant future where AI automates image protocoling and acquisition,



optimizing its value. In addition, AI software could even “read” every case and prefill a preliminary report, complete with highlighted findings, for delivery to the radiologist.

The radiologist’s role would be to validate the report, much like it is done in systematic peer reviewing of residents’ preliminary reports. This workflow could increase productivity and give radiologists more time to spend on complex matters and less time on simple and repetitive tasks.

It’s like the autopilot system on an aircraft. Piloting an airplane is complex and requires completion of many checks and activities, some of which are simple but tedious . The autopilot takes over some of those duties so that under the pilot’s supervision, the system controls almost every part of the flight, freeing the pilot to devote their work time on more essential and critical work, cross-checks, and verifications.

Similarly, radiologists supported by AI working in the background, preparing materials and optimizing workflow, could retain their essential roles but spend more time on complex or ambiguous cases while continuing to deliver high-quality reports to referring physicians.

Studies have shown that radiologists have a day-to-day average error rate of 3 to 5%.[10] This rate is rising with the growing volume of work,[11] increasingly difficult working conditions, and high burnout rate faced by today’s radiologists.

Peer review at the image and report levels can minimize error rates; however, the reality is that not enough radiologists are available to peer review every case and ensure optimal quality. Artificial intelligence has the potential not only to significantly improve the performance of reporting,[7] but also to work 24/7 to achieve the goal of zero errors in radiology.

I wouldn’t be surprised if the use of qualified AI software becomes a requirement for reimbursement, as is already the case with respect to validation of the appropriateness of advanced imaging requests by qualified electronic clinical decision support system under the Protecting Access to Medicare Act (PAMA) of 2014 in the USA.[12] Considering current research and investment, these scenarios are more likely than ever.[13-15]

It is also worth noting that key healthcare players outside of radiology can find significant value in AI for imaging interpretation, particularly at the point of care.[16] Equipping these caregivers with AI-generated reports can pave the way to new workflows and more efficient patient care pathways and has the potential to become essential to care provided outside of radiology.

Indeed, portable ultrasound and MRI devices can extend the capabilities of front-line healthcare professionals only so long as the clinicians are able to understand their results. Artificial intelligence-powered

software can provide them with the necessary guidance and information right where they are required.[17-20] Imaging at the point of care extends AI-based radiology's market value far beyond our field and will certainly strengthen its status as a must-have in the healthcare ecosystem.

Medicine is rapidly moving toward early multimodal diagnosis and personalized care,[21] aiming at better outcomes by delivering the right therapy to the right patient at the right time. Medical imaging is a key pillar in this new era,[22] and AI is arguably its most important catalyst.

Ultimately, I believe that by systematically extracting insights from images that are impossible to detect by human eyes and combining them with other data, AI has the potential to become a must-have weapon in the growing arsenal of healthcare technology.

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Surfactant Protein C Deficiency-associated Diffuse Lung Disease

Ankita Chauhan, MD; Preet K Sandhu, MD

Case Summary

A teenager with known surfactant protein C deficiency and restrictive lung disease, who was extremely sick as an infant, presented with shortness of breath, exercise intolerance, chest pain, palpitations, and severe pectus excavatum (PE) deformity. Echocardiography showed external compression of the right atrium and right ventricle that was hemodynamically insignificant. Flexible bronchoscopy revealed pulsatile, 40-50% extrinsic compression of the left mainstem bronchus anteriorly. They had undergone an extensive workup for hypoxemia and failure to thrive as an infant, including a lung biopsy at four months of age that showed findings of chronic pneumonitis of infancy. Genetic testing revealed the diagnosis of Surfactant Protein C (SP-C) deficiency.

Imaging Findings

Neonatal chest radiographs showed diffuse haziness in both lung fields. The lungs demonstrated diffuse prominent interstitial markings on the chest radiographs obtained as a toddler with follow-up radiographs showing progressive interstitial lung disease in a bilateral interstitial reticulonodular pattern (Figure 1). With age, the interstitial lung markings became coarser.

Computed tomography (CT) of the chest obtained in childhood revealed multiple, small, thin-walled cysts throughout the lungs. Follow-up CT obtained in early adolescence redemonstrated multiple, randomly distributed, thin-walled cysts in both lungs with interval new ground-glass attenuation areas in bilateral lower lobes (Figure 2). There was progressive interstitial thickening and fibrosis with age, predominantly involving bilateral lower lobes. There were no focal areas of consolidation to suggest bronchiolitis obliterans. The imaging features represent chronic cystic interstitial lung disease due to surfactant deficiency.

Additionally, PE deformity and thoracic spinal scoliosis developed and then worsened with age. There is a known association of PE with congenital cystic lung disease, the former being characterized by depression of the anterior chest wall, resulting in cardiopulmonary compression symptoms and restricted pulmonary ventilation disorders.[1] Severity of PE is assessed by the Haller index (HI), which is calculated by dividing the maximum transverse diameter of the chest by the distance between the posterior surface of the sternum and the anterior surface of the vertebra. This is typically measured on the axial CT slice with the shortest distance between the two. An HI greater than 3.25 indicates severe PE (normal being 2.0 or less). In this patient it was 5.4 (Figure 3). Surgical correction of PE is warranted in symptomatic patients with a high HI. Our patient underwent a minimally invasive procedure with substernal placement of a concave bar (Nuss bar).

Owing to the patient's tall height and PE, they were evaluated for Marfan syndrome; however, the criteria for Marfan disease were not met.

Diagnosis

Surfactant Protein C Deficiency-associated diffuse lung disease

Discussion

Childhood interstitial lung disease (ChILD), a subset of pediatric diffuse lung disease (DLD), is a heterogeneous

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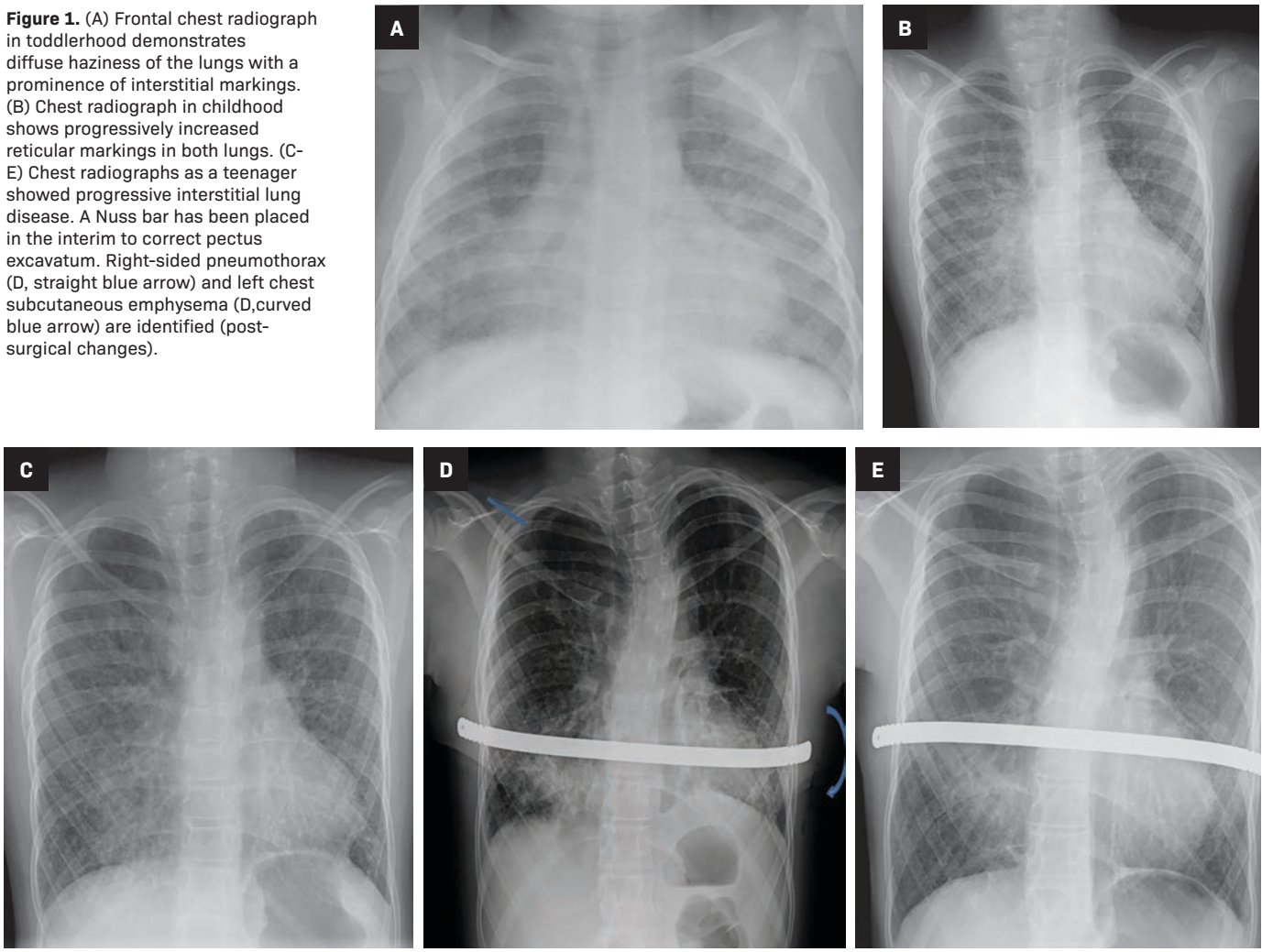


Figure 1. (A) Frontal chest radiograph in toddlerhood demonstrates diffuse haziness of the lungs with a prominence of interstitial markings. (B) Chest radiograph in childhood shows progressively increased reticular markings in both lungs. (C-E) Chest radiographs as a teenager showed progressive interstitial lung disease. A Nuss bar has been placed in the interim to correct pectus excavatum. Right-sided pneumothorax (D, straight blue arrow) and left chest subcutaneous emphysema (D,curved blue arrow) are identified (post-surgical changes).

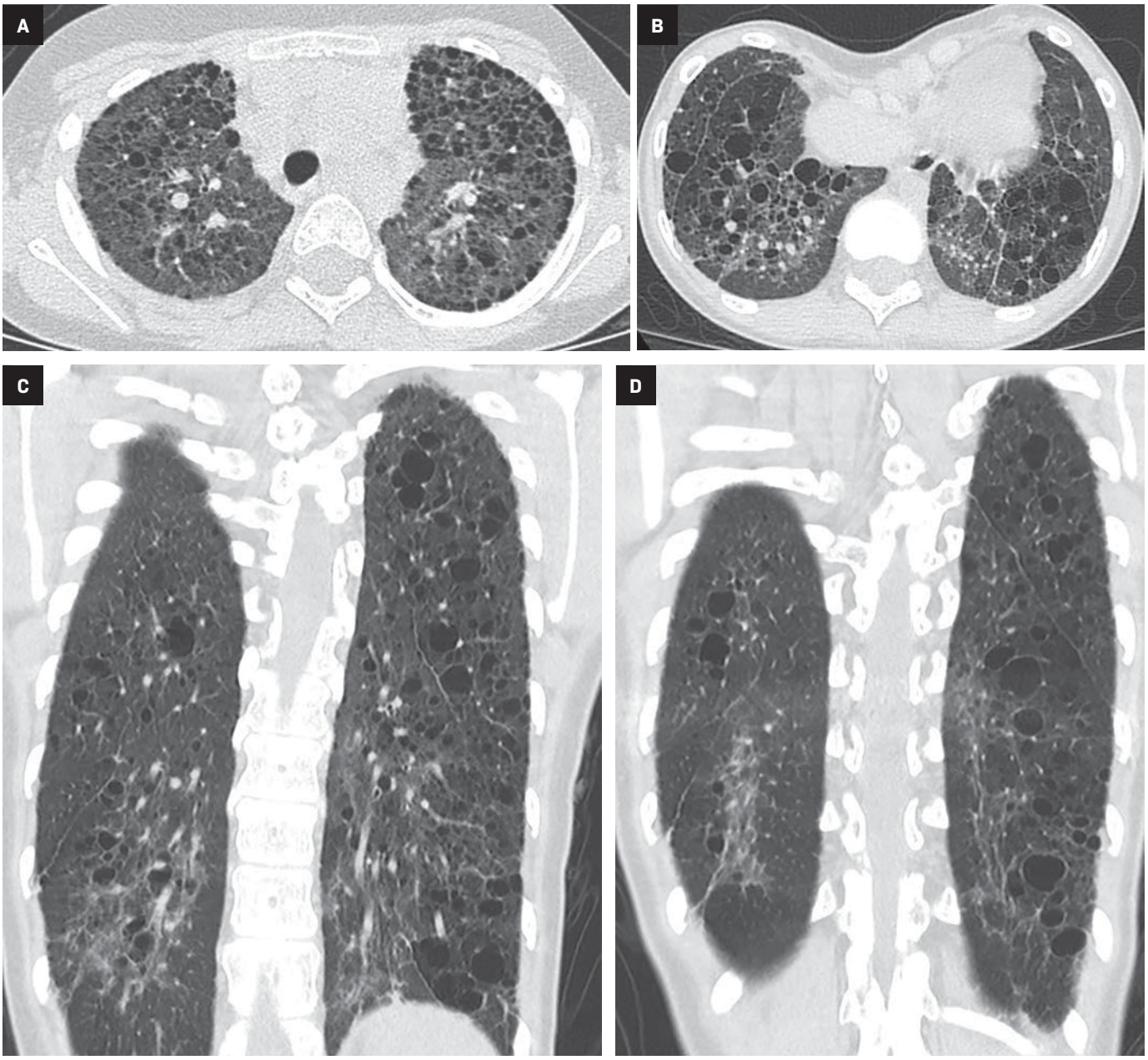
group of rare childhood respiratory diseases. In children younger than 2 years of age, the term DLD is preferred over ChILD until other more common causes of DLD are excluded, and diagnosis of ChILD is confirmed.[1] Although they are termed "interstitial lung diseases," these conditions are not limited to the interstitium and can involve the alveoli, airways, lymphatics, blood vessels, and pleural spaces.[1,2] ChILD conditions have a different etiologies to those of adults with ILD.[3]

The most common clinical sign in ChILD is tachypnea (75-93% of cases).[2,4] Other signs include cough, failure to thrive, crackles, or wheezing. Before a child can be diagnosed with a ChILD syndrome, other causes such as congenital heart disease, congenital or acquired immunodeficiency syndromes, asthma, cystic fibrosis, primary ciliary dyskinesia, infection, and recurrent aspiration should be excluded. Three of the following four criteria should also be present: respiratory symptoms (cough, rapid breathing, difficulty in breathing, or exercise intolerance); respiratory signs (retractions, resting tachypnea, adventitious sounds, failure to thrive, digital clubbing, respiratory failure); hypoxemia; and diffuse abnormalities on chest radiograph or CT scan.[2,4]

ChILD associated with an autosomal dominant mutation in the SP-C gene was first described in 2001 by Nogee, et al.[5] About 10% of pediatric DLD is caused by surfactant metabolic dysfunction.[6,7] SP-C has a role in surfactant function to reduce surface tension and prevent end-expiratory atelectasis.[2,3] Lung disease caused by different SP-C mutations varies greatly, from respiratory distress syndrome (RDS) in neonates to ILD in adults.[7,8] Studies have revealed an earlier age of onset and a more prevalent failure to thrive in a group with SP-C mutations.[7] Superimposed lung infection in infants, particularly respiratory syncytial virus, can result in respiratory failure and worsening interstitial lung changes.[8]

Imaging findings on chest radiographs include hazy granular pulmonary opacities in patchy or diffuse distribution. Lung volumes are usually normal to low; however, they may be increased with assisted ventilation.

Figure 2. (A) Axial CT image of the chest in lung algorithm in childhood shows diffuse ground-glass opacities and superimposed innumerable cysts. (B) Axial CT chest in lung window in adolescence shows an increase in size and number of the thin-walled parenchymal cysts. Note the pectus excavatum, (C-D) Coronal CT images of the chest in lung algorithm in early adulthood redemonstrated interstitial lung disease with lower lobe fibrosis and innumerable thin-walled cysts throughout the bilateral lung fields. There has been mild interval enlargement of multiple cysts.



High-resolution CT findings include diffuse or patchy ground-glass opacities, consolidation, interlobular septal thickening, lung cysts, and paraseptal cysts. Regression of ground-glass opacities occurs with increasing patient age and development of lung cysts and septal thickening.[1,4] Pectus excavatum may be seen in older children and is thought to be related to abnormal chest wall development in the setting of restrictive lung disease.[1,5]

Although the CT findings are nonspecific, CT can be helpful in several ways. It helps define the extent of disease, for following disease progression, guiding biopsy, and excluding other causes of clinical symptoms. Chest CT is also valuable for monitoring the effects of treatment, as there is a strong correlation between clinical improvement and CT findings.[8]

In the past, lung biopsy has been the diagnostic gold standard despite the potential complications. However, identifying the genes responsible

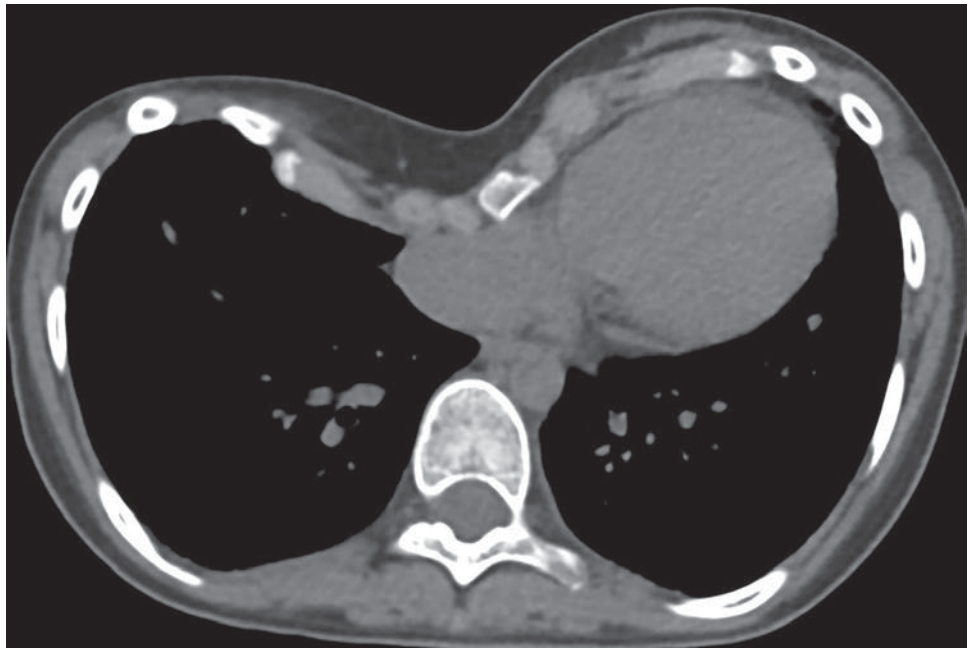


Figure 3. Axial CT in soft-tissue window shows progressive posterior depression of the sternum resulting in a reduction of the AP diameter of the chest.

for surfactant dysfunction disorders avoids the need for a biopsy in approximately 10% of children.[7] With the broader availability of genetic testing, ILD CT imaging patterns may sufficiently suggest a diagnosis, thus avoiding the need for a surgical lung biopsy.[2] Surgical lung biopsy using video-assisted thoracoscopy is recommended for infants with clinical urgency to identify the specific form of pediatric ILD or in whom other diagnostic evaluations have not yielded a specific diagnosis.[2] Hence, an interdisciplinary clinical, radiological, and histopathological consensus is currently the gold standard.[9,10]

Conclusion

Surfactant Protein-C deficiency is a rare lung disease with highly variable age of onset, severity, and natural history. It varies greatly, from RDS in neonates to ILD in adults. An interdisciplinary clinical, radiological, and histopathological consensus is currently the diagnostic gold standard. HRCT imaging patterns of ILD may sufficiently suggest a diagnosis that can be confirmed by genetic testing and avoid the need for a surgical lung biopsy.

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Bronchoesophageal Fistula

Christopher Zarour, MD, RPVI; Ramzi Ibrahim, MD; Arooj Mian, MD; Mohammed Al-Hameed, MD; Barakat Ogunde, MD; Grygori Gerasymchuk, MD

Case Summary

An adult with a 20 pack-year history of smoking and essential hypertension presented to the emergency department with complaints of intermittent, sharp, nonradiating epigastric and substernal pain of one month's duration. Other symptoms included increasing dysphagia, decreased appetite, and 10 lb weight loss over one month. There was no alleviation with antacids. The patient denied fever, night sweats, and shortness of breath. Initial laboratory evaluation showed leukocytosis at approximately 14,000; hyponatremia at 133; and hypochloremia at 96. An electrocardiogram demonstrated sinus tachycardia with possible left atrial enlargement and left ventricular hypertrophy. Troponins were negative.

Imaging Findings

Initial chest radiography was unremarkable. Esophagogastroduodenoscopy and esophagogram confirmed the diagnosis of an ulcerated, annular mass in the esophagus with fistulous communication to the medial segment bronchus of the right lower lobe.

Contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis demonstrated a long segment of circumferential wall thickening measuring 1 cm in the mid-esophagus. A tract was seen extending from the mid-esophagus to a right lower lung cavitation, demonstrating an irregularly thickened wall and measuring 2.5 x 5 x 7 cm (TR x AP x CC). Ground-glass opacities surrounded the right lung cavity (Figure 1).

Follow up esophagram with water-soluble contrast demonstrated contour irregularity of the mid-esophagus with contrast extravasation to the right bronchial tree (Figure 2).

Diagnosis

Bronchoesophageal fistula

Discussion

A bronchoesophageal fistula (BEF) is an abnormal connection that forms between the esophagus and the bronchus, most commonly within the right bronchial tree.[1] Bronchoesophageal fistulas may be congenital or acquired, with acquired causes being more common.[1,2] They include trauma, malignancy, infection, prior thoracic surgeries, silicosis, foreign body ingestion, esophageal diverticulum, or prolonged endotracheal intubation.[1,3,4] In a case such as the one described here, a significant history of smoking seemed to be a major contributor to the development of esophageal malignancy. Other risk factors associated with malignancy of the esophagus include hot fluids, alcohol, caustic ingestion, and achalasia.

Congenital causes of BEF are less common and typically appear in the neonatal period, although presentation during adulthood has been reported.[5] Congenital BEFs may present with normal mucosal lining within the fistula, unlike the acquired etiologies, which show absence of the normal mucosal lining.[6]

These entities were initially described in 1965 with a classification system that remains in use today. Type 1 BEFs consist of an esophageal diverticulum forming the fistula, type 2 consist of an extension of the esophagus into a lobar or segmental bronchus (most common), type 3 result from an extending bronchogenic cyst, and type 4 results from a pulmonary sequestration.[1,7]

Bronchoesophageal fistulas are rare, with very few reported in the

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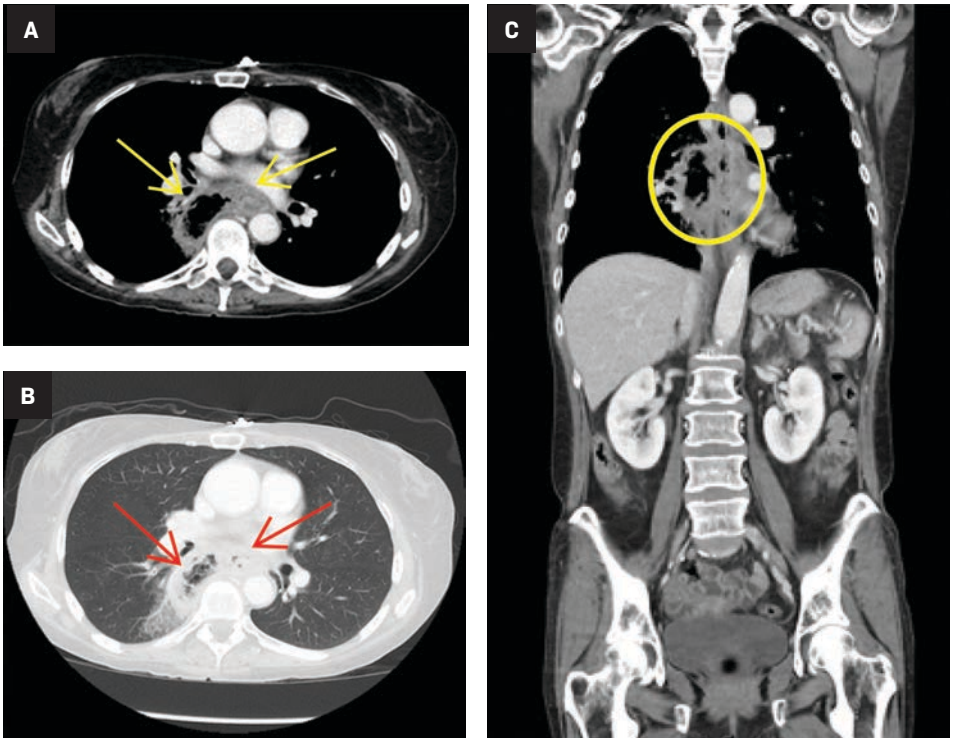

Figure 1. (A-C) Axial and coronal contrast-enhanced CT scans of the chest, abdomen, and pelvis demonstrate a necrotic esophageal mass with a tract to the pulmonary parenchyma.

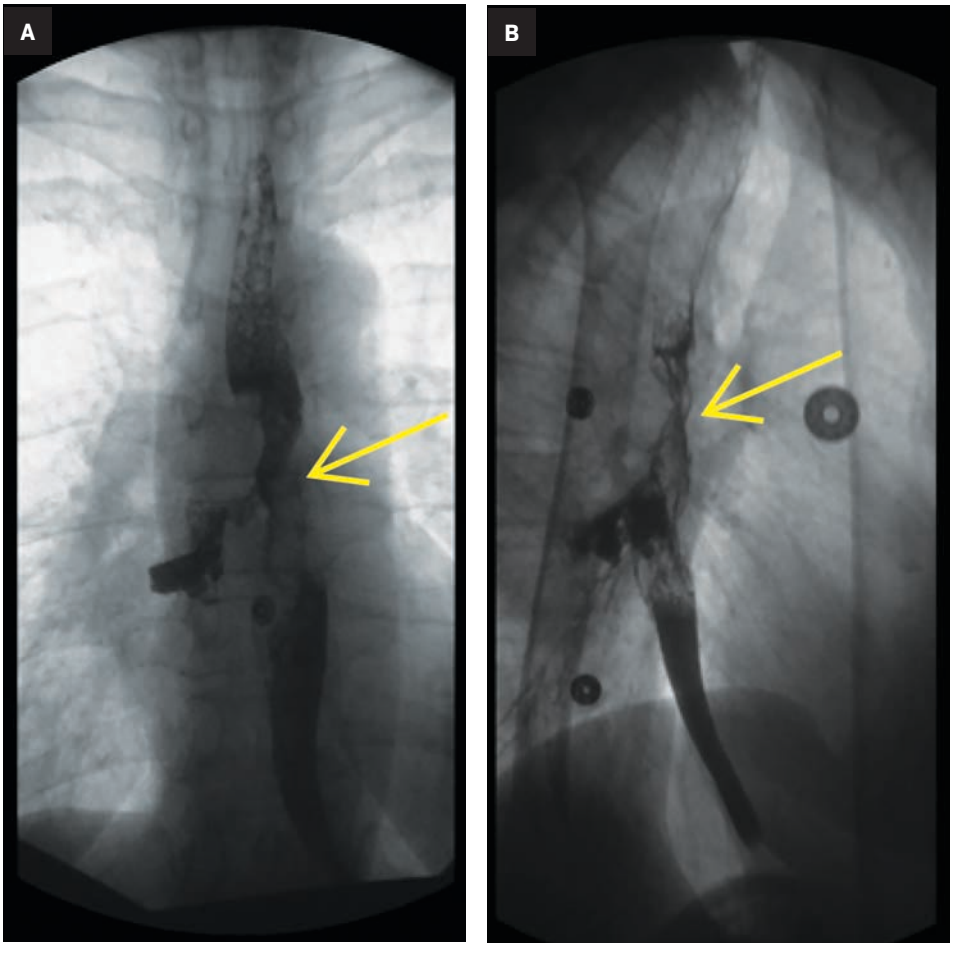

Figure 2. (A,B) Frontal and LPO single contrast-enhanced esophagram demonstrates the esophageal mass with a fistula to the right bronchial tree.

medical literature. Diagnosis is commonly delayed or potentially misdiagnosed, whereas tracheoesophageal fistulas, which have a higher incidence and greater association with endotracheal intubation, are typically diagnosed much more quickly.[1,6] Delays in diagnosis are usually due to the condition's nonspecific presentation; common signs and symptoms at presentation are chronic cough, hemoptysis, signs of aspiration, dysphagia, abdominal or chest pain, or worsening gastroesophageal reflux.[7] Delays in diagnosis are more common among benign causes than malignant cases, owing to the mild nature of pathology in the former. Conventional esophagography is considered the gold standard test for diagnosing BEF, although endoscopy can also be easily used to visualize an esophageal mass.[1,3]

Bronchoesophageal fistulas are associated with a high morbidity and mortality, and the underlying cause should be investigated. Timely treatment should be initiated to avoid sepsis and aspiration.[1,3] Surgical treatment, which consists of excision of the fistula with closure of the abnormal openings, has a high rate of success.[1,8] Alternative treatments include either surgical stapling or applying acetic acid and sodium hydroxide to both ends of the fistula.[9,10] In cases associated with an underlying malignancy, palliative care may be performed with esophageal stenting.

Conclusion

Acquired BEFs are less common than tracheoesophageal fistulas. While underlying causes vary, malignancy-associated BEFs tend to present with nonspecific, vague symptoms that require further work-up. Once diagnosed, treatment of BEF typically consists of surgical excision unless high-grade malignant cases necessitate palliative care.

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Iatrogenic Neonatal Calcinosis Cutis

Chelsea Sparks, MD; Irmel Ayala, MD; Alexander J Towbin; MD, Richard B Towbin, MD; Jennifer Kucera, MD

Case Summary

A premature neonate presented to the emergency department at several weeks of age, for evaluation of a right arm mass, which was present for several days (Figure 1). The infant was afebrile and alert. The mass was located at the right antecubital fossa and was erythematous, nodular, and firm. Laboratory results on arrival revealed no leukocytosis or neutrophilia. The neonate had been discharged from the neonatal intensive care unit (NICU) several days before the appearance of the mass. In the NICU, the patient had been treated for hypocalcemia with calcium gluconate via peripheral IV placed in the right antecubital fossa.

Imaging Findings

Sonographic images demonstrated a well-circumscribed, heterogeneous mass containing calcification with posterior shadowing and no abnormal internal vascularity (Figure 2). The cephalic and basilic veins were hyperechoic with posterior shadowing consistent with complete calcification, and a small, partially calcified, nonocclusive thrombus was seen in the right subclavian vein. Right humeral radiography demonstrated a calcific density in the antecubital region with high density material coursing along a path suggestive of venous structures, confirming the sonographic findings of the calcified cephalic and basilic veins (Figure 3).

Diagnosis

Iatrogenic neonatal calcinosis cutis. Differential diagnosis based on the imaging findings include subcutaneous fat necrosis of the newborn, subepidermal calcified nodule, osteoma cutis, pilomatricoma (calcifying epithelioma of Malherbe), and pseudoxanthoma elasticum.

Discussion

Calcinosis cutis results from the deposition of insoluble calcium salts into the skin and subcutaneous tissues. It can be separated into five subtypes: dystrophic calcification, metastatic calcification, calciphylaxis, idiopathic calcification, and iatrogenic calcification.[1] Dystrophic calcification presents with cutaneous ectopic calcified masses composed of hydroxyapatite and calcium phosphate. Necrotic cells with denatured phosphate bound proteins become a nidus for calcification while altered collagen and elastin also facilitate calcification.[2] High mitochondrial calcium and phosphate levels contribute to subsequent crystal deposition and necrosis, which results in a more acidic environment. Increased acidity subsequently interferes with calcification inhibitors.[3]

Dystrophic calcification is classically seen in connective tissue disorders; however, it can also manifest after local tissue injury or within tumors. Localized dystrophic calcification can be seen in scleroderma, while widespread calcification can be seen in juvenile dermatomyositis and is termed calcinosis universalis.[3]

Metastatic calcification results from abnormally elevated serum calcium or phosphate levels, which cause calcium salt precipitation in normal tissue. Milk alkali syndrome, excessive ingestion of calcium-containing foods or antacids, or hypervitaminosis D may result in metastatic calcification with cutaneous lesions regressing if serum calcium levels return to normal limits.[4]

Calciphylaxis is characterized by mural small-vessel calcification, predominantly within the subcutaneous fat or dermis, which leads to vasculopathy and eventually ischemia

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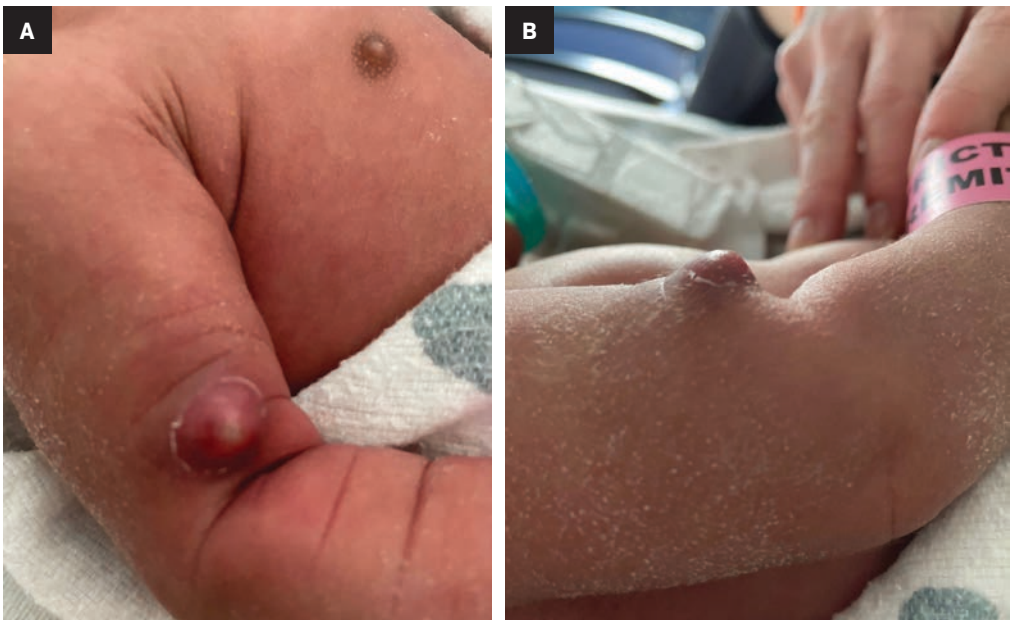
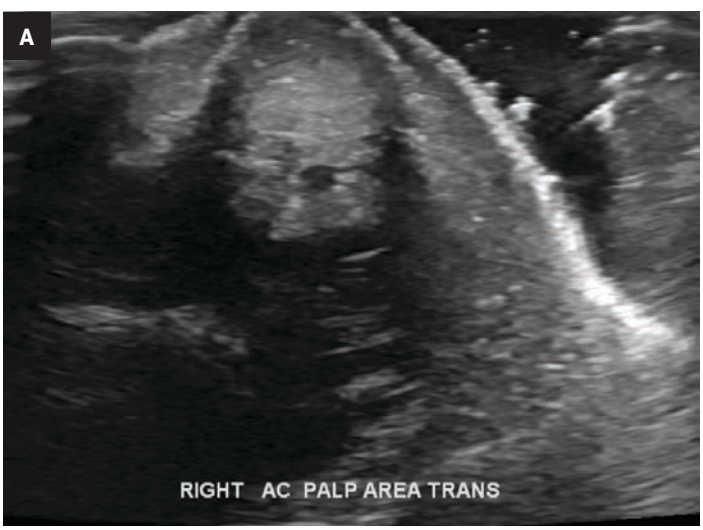
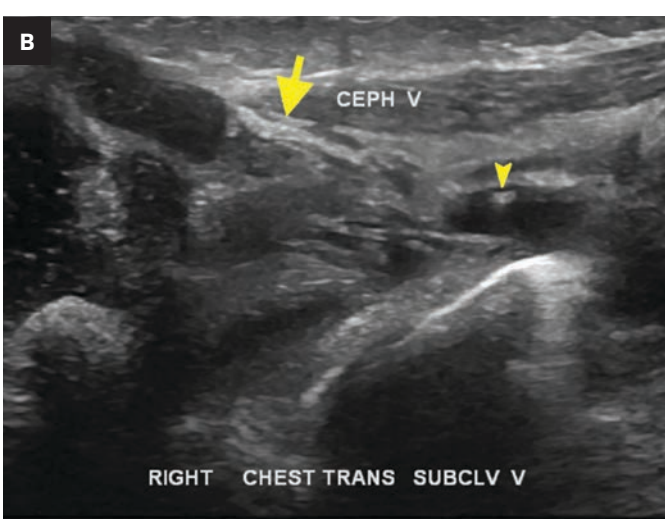


Figure 1. (A,B) Firm, nodular, erythematous lesion at the right antecubital fossa measuring. The lesion demonstrates yellow-white coloration centrally.





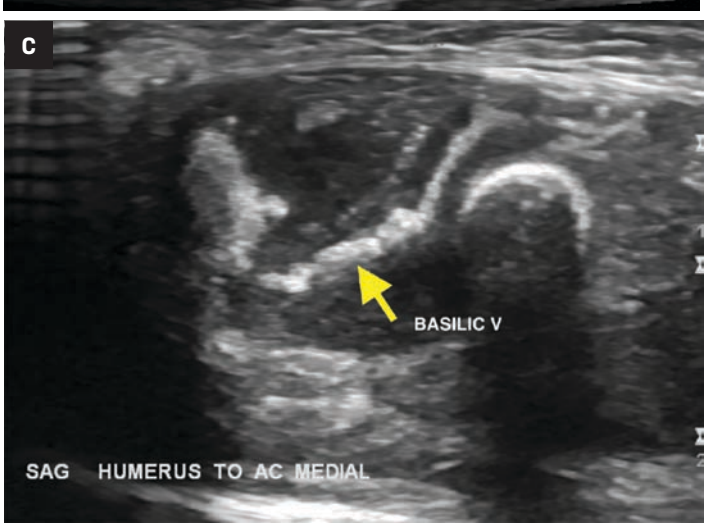
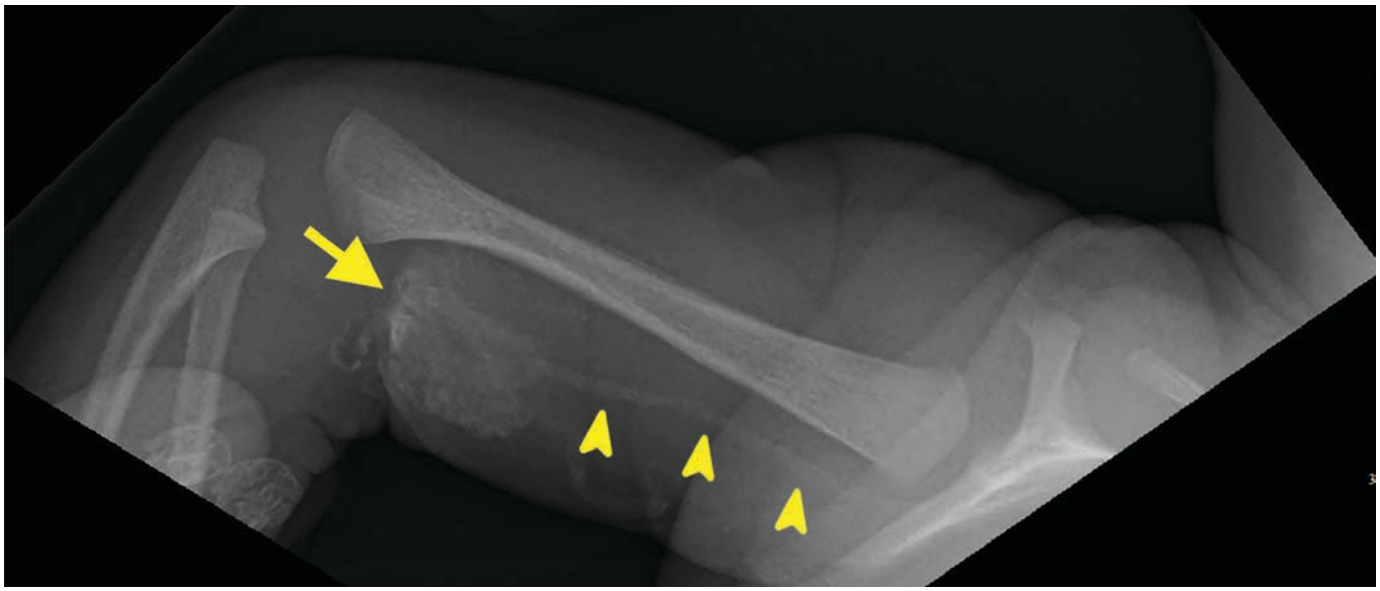


Figure 2. (A) Sagittal ultrasound of the right antecubital fossa demonstrates a heterogeneous, rounded nodule with internal echogenic foci suggestive of calcification with posterior shadowing. (B.C) Transverse ultrasound through the right upper arm and lower chest demonstrating the central cephalic vein (arrow), with linear hyperechoic regions surrounding the vessel, consistent with calcification. Nonocclusive thrombus within the right subclavian vein is also seen (arrowhead).

Figure 3. Right humeral radiograph depicts a calcific density in the antecubital region (arrow) with radiodense material coursing along a path suggestive of venous structures (arrowheads), analogous to the sonographic findings of the calcified cephalic and basilic veins.



or infarction of the supplied tissue. Extravascular calcium deposits may also occur.[5] Calciphylaxis most often presents in patients with end-stage renal disease; however, it has also been described in patients with normal renal function with primary hyperparathyroidism.[6]

The absence of an identifiable metabolic disorder, tissue damage, or therapy characterizes the idiopathic subtype. An example of idiopathic calcinosis cutis is tumoral calcinosis, a condition typified by the deposition of calcium around major joints in adolescents without underlying conditions or altered calcium metabolism.[1]

The iatrogenic subtype is usually seen as a side effect of therapy and has been reported to occur following the administration of intravenous calcium gluconate for hypocalcemia.[7-13] In our patient, further testing revealed the mother to be vitamin D deficient, a risk factor predisposing newborns to neonatal hypocalcemia.[11]

Iatrogenic calcinosis cutis can develop after extravasation of calcium at a venipuncture site.[1] Damaged subcutaneous tissue and resulting cell necrosis at the site of the extravasation creates a more acidic environment that lacks calcification inhibitors, facilitating precipitation.[4] Multiple white-yellow cutaneous papules or nodules with erythema or necrosis develop within 3 weeks of the initial soft tissue injury.[12]

Calcification may also occur along blood-vessel sheaths from the extravasated material. In our patient, thrombosis was attributed to venous stasis resulting from calcification. Intravenous therapeutic calcium solutions are not radiodense; thus, radiographs do not typically show subcutaneous calcification until approximately 2 weeks following extravasation. Treatment options have included elevation, cold compresses, local surgery, the topical glucocorticoid triamcinolone, and diltiazem, a calcium channel blocker. In most cases, the calcification begins to clear at 8 weeks, with resolution occurring by 6 months.[7]

Subcutaneous fat necrosis of the newborn (SCFN) is one of the entities in the differential diagnosis for a subcutaneous lesion in neonates. It is a transient disorder of the subcutaneous adipose tissues, most often occurring in infants with hypoxia or perinatal stress and is characterized by firm subcutaneous nodules.[14] The mechanism of SCFN is currently unknown; however, SCFN is postulated to occur from a combination of local tissue hypoxia and mechanical stress and/or the enrichment of saturated fatty acids, which increases the tissue propensity for crystalization.[15]

Hypercalcemia can be seen in up to 25% of SCFN cases.[16] While the proposed mechanisms of SCFN differ from iatrogenic calcinosis cutis, lesions may appear sonographically similar. Additionally, subepidermal calcified nodule is a differential consideration for a solitary nodule within this demographic. However, the former typically occurs in the head or neck and is classified as an idiopathic calcinosis cutis. Clinical history is essential in making the correct diagnosis in these cases.

Conclusion

Calcinosis cutis occurs when insoluble calcium salts are deposited

in the skin and subcutaneous tissues. Neonatal iatrogenic calcinosis cutis is rare but can be seen in neonates in the setting of prior intravenous calcium gluconate administration and may be suspected with appropriate historical findings, such as a history of neonatal hypocalcemia.

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Jejunal Atresia

Jason K Lee, BSRT(R) CT RA, RPA; Jennifer K Son, MD; Melissa R Spevak, MD

Case Summary

An infant born at 35 weeks' gestational age was diagnosed prenatally with small bowel obstruction via ultrasonography and fetal magnetic resonance imaging (MRI). Given the bowel obstruction and significant output of bilious fluid, a nasogastric tube was placed shortly after birth. At day 2 of life, the infant underwent a fluoroscopic upper gastrointestinal (UGI) series with small-bowel follow through (SBFT). A genetic workup and a complete abdominal ultrasound were also performed to evaluate for other anomalies prior to surgical repair.

Imaging Findings

Fetal MRI performed at 28 weeks' gestational age demonstrated multiple fluid-filled and dilated loops of bowel in the left upper abdomen with some extension into the right abdomen (Figure 1). Residual distal loops of bowel and colon were decompressed. Abdominal radiography performed shortly after birth revealed a gas-filled stomach and dilated duodenum and proximal jejunum with a suction catheter present (Figure 2).

Subsequent UGI with SBFT demonstrated a distended duodenum and proximal jejunum that abruptly ended in the right abdomen, with a complete paucity of bowel gas distally (Figure 3). Delayed (100-min) abdominal radiography demonstrated the lack of contrast progression (Figure 4). Abdominal ultrasound revealed a dilated, fluid-filled duodenum and dilated loops of proximal jejunum, with the remaining abdomen appearing unremarkable (Figures 5, 6).

Subsequent exploratory laparotomy revealed a proximal jejunal atresia with two additional distal atretic segments, plus an "apple peel" deformity. The first atresia was noted to be located 12 cm distal to the ligament of Treitz.

Diagnosis

Jejunal atresia

Discussion

Atresia, considered one of the most common causes of congenital bowel obstruction, is characterized as a congenital defect that results in complete obstruction of the lumen.[1] Jejunal and/or ileal atresia is present in 1 in 3,000-5,000 births and constitutes approximately 39% of all intestinal atresias.[2] Jejunoileal atresia results from an ischemic insult during pregnancy; the injury can be secondary to intussusception, perforation, volvulus, intestinal strangulation via hernia, or thromboembolism. Additional factors such as maternal smoking and cocaine use have also been associated with intestinal atresia.[3]

Newborns typically present with feeding difficulties, bilious vomiting, distended abdomen, and absence of bowel movements.[4]

Although ultrasound is the imaging modality of choice for screening and preliminary identification of fetal abnormalities, MRI evaluation of the fetal gastrointestinal tract is increasingly utilized.[2] Postnatally, fluoroscopic contrast studies can be helpful in assessing

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Figure 1. Coronal T2 HASTE image from the fetal MRI shows multiple fluid-filled and dilated loops of bowel predominantly in the left hemi-abdomen.

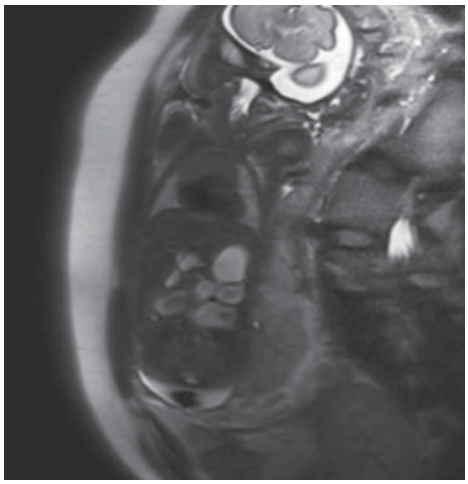


Figure 2. Anteroposterior supine abdominal radiograph reveals a prominently dilated loop of bowel within the central abdomen, likely in the jejunum, with the nasogastric tube terminating in the stomach.

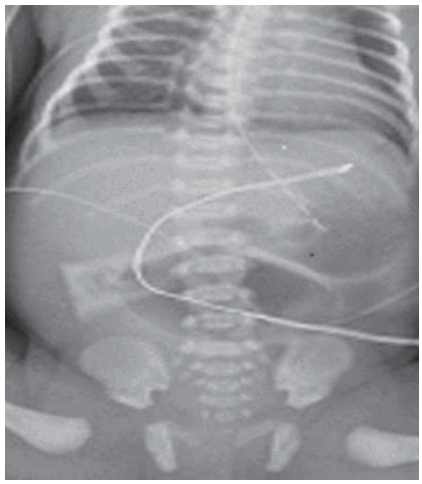


Figure 3. Abdominal radiograph performed at the end of the UGI series demonstrates moderately distended, contrast-filled proximal jejunal loops.

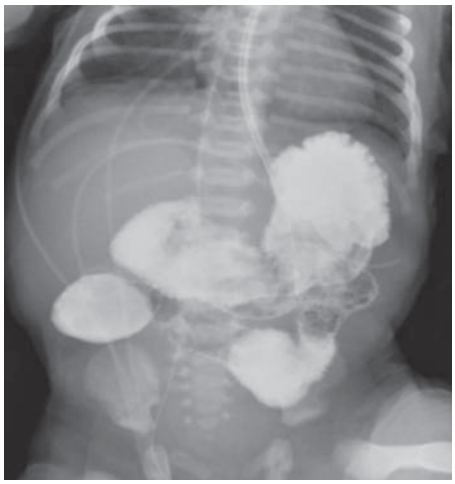


Figure 4. Abdominal radiography 100-mins following upper GI demonstrates contrast remaining within a dilated jejunal loop of bowel. There is a lack of contrast progression into more distal bowel loops, consistent with jejunal atresia.

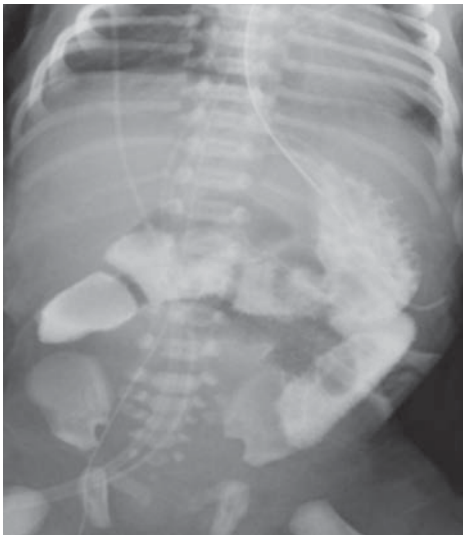
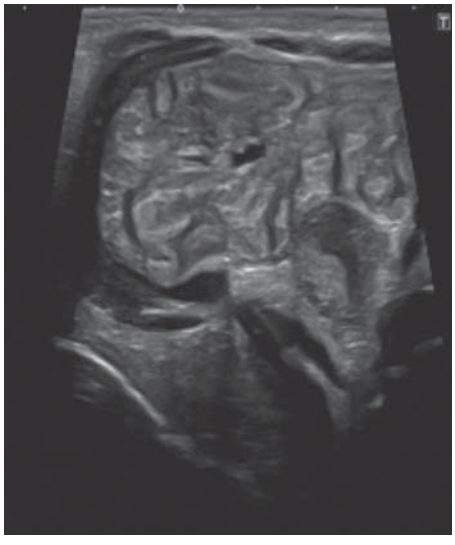


Figure 5. Transverse image obtained during the abdominal ultrasound shows a dilated duodenum

Figure 6. Transverse abdominal ultrasound image shows the remaining small bowel to be completely decompressed, compatible with small-bowel atresia.



the location and type of obstruction prior to surgery.

Conclusion

Atresia is a common form of bowel obstruction that appears as an abrupt, rounded end to a lumen. Early diagnosis and prompt surgical intervention is key to avoiding bowel ischemia and restoring continuation of bowel.

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"The object of a New Year is not that we should have a new year. It is that we should have a new soul and a new nose; new feet, a new backbone, new ears, and new eyes."
—GK Chesterton

Happy New Year!

C Douglas Phillips, MD, FACR

Chesterton loved a verbal exchange; the chance to debate and both speak and listen. I think he would be horrified to see the current status of the US re: political discussion. I'm with him.

Enough politics. At the end of another year (and start of a fresh one) I find it nearly impossible to veer off my typical path to think about the past. The "Wet Read Historical Moment". Our topic for today is, drum roll please … **Professional courtesy**.

I am going to imagine that many of you younger types don't know what I'm talking about. Allow me to educate you. In the old days (pre-crazy insurance, bottom line, venture capital-owned imaging centers, etc), there was a certain agreement. Hard to call it a rule, because sometimes people didn't play along (and oh, Lord, how we all knew and hated **those** people).

But we had this physician-to-physician agreement that we didn't bill a comrade-in-arms for services. Or, we billed what their insurance would pay and refused to accept another cent. If their insurance didn't pay, didn't matter. We didn't even barter. No, we don't need another bottle of wine. Just did it for free. I can distinctly remember seeing physicians after I finally became one and marveling at the idea. What? No bill? I participated, too. We could dictate "professional courtesy" and the staff closed the matter. Sigh. Like many others, another tradition has bitten the dust.

For those with gray hair, can you remember the first time you got billed? Why, the hubris of that person! I'll make sure I bill them next time! And then, within years, the whole idea of professional courtesy just went away. I guess it was a matter of time, or perhaps a matter of finances. I can only speak to our industry, but as I understand it, the same thing has gone on around us. Barbers used to cut each other's hair for free (and as a piece of advice, in a barbershop with just two barbers, use the one with the crappy haircut, because the other one cut **their** hair). I hear barbers bill each other now, as well. I wonder if that has led to getting rid of partners who charged you for a bad cut?

I suppose it is a matter of fairness. Or just the further coarsening of society and a loss of collegiality. Hard to say for sure. It was a nice little perk, and it gave you another reason to be happy to be a doctor. It also allowed you to be nice to your colleagues in a very tangible way.

Find another way to be nice to your colleagues. Stay well, have a great New Year, and keep doing that good work. Mahalo.

Dr Phillips is a Professor of Radiology, Director of Head and Neck Imaging, at Weill Cornell Medical College, NewYork-Presbyterian Hospital, New York, NY. He is a member of the *Applied Radiology* Editorial Advisory Board.

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