Chapter 1
Imaging Modalities and Contrast Agents

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Introduction

This chapter discusses the spectrum of available imaging studies employed in routine diagnostic imaging. Many of the associated advantages, deficiencies, concepts, and applications covered here can guide referring clinicians in selection of the appropriate imaging modality across organ systems, i.e., neurologic, cardiothoracic, gastrointestinal, genitourinary, vascular, and musculoskeletal (MSK). Regardless of the organ system, the choice of the appropriate study depends on multiple factors, including the clinical question to be addressed, the availability and accuracy of the imaging modality, study contraindications, risks of the imaging examination including those from contrast agent administration, and financial cost. Some very brief data regarding the Medicare reimbursements for several commonly ordered imaging examinations is also provided at the end of the chapter (Table 1.1).

It is important for clinicians to understand how contrast agents apply to imaging. Basic familiarity with common indications, significant contraindications and potential complications of contrast media use are essential for optimal patient care. We discuss the indications, contraindications, and risks of contrast agents that are routinely used in clinical practice today. This knowledge may be reinforced, and at times supplemented by radiologists in their role as consultants who are part of the medical team charged with quality diagnostic imaging management.

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Table 1.1 2012 Medicare reimbursement for various imaging modalities

Imaging modality	Reimbursement ($)[a]
CR	35
Skeletal survey	75
US limited (mass)	45
US complete (tendons, muscles, etc.)	130
CT (w/o, w/)	245–300
BS	275
BS (3 phase)	315
Labeled WBC study	375
MRI (w/o, w/ and w/o)	430–675
PET/CT	1,225

[a]2012 Medicare fee schedule: combined professional and technical fees (global fee)

Imaging Modalities

Overview

The most commonly used imaging technologies include conventional radiography (CR), computed tomography (CT), ultrasound (US), magnetic resonance imaging (MRI), and a variety of nuclear medicine studies (NM), each with a specific purpose (Table 1.2). While CR is typically a starting point for most evaluations in the chest, abdomen, and MSK system, this is not always the case. For example, soft tissue pathology generally is better evaluated by more advanced techniques, particularly MRI, US, and at times CT.

Conventional Radiography

Radiographs serve as the starting point in the imaging diagnosis of many categories of suspected pathology, e.g., pneumonia and congestive heart failure in the chest, small bowel obstruction and suspected free intraperitoneal air in the abdomen and especially for trauma, osteomyelitis, focal mass lesions, and arthropathies in the MSK system. Plain radiographs are inexpensive, widely available, and rapidly obtainable, even at the bedside if necessary. Disadvantages of radiographs include ionizing radiation and low contrast resolution making them unable to visualize most soft tissue abnormalities.

Ultrasound

US is less expensive than CT, MRI, and NM. In addition, it does not expose the patient to ionizing radiation, an important consideration particularly in children and

Table 1.2 Common diagnostic imaging modalities

Imaging modality	Advantages	Disadvantages and limitations
Conventional radiography (CR)	Very inexpensive	Ionizing radiation
	Universally available	Low contrast resolution
	Quickly obtained	Limited evaluation of soft tissues
		Projectional superimposition (2-D representation of 3-D anatomy and pathology)
Ultrasound (US)	Relative low cost (vs. CT, MRI, NM)	Operator-dependent
	No ionizing radiation	Limited availability of well-trained, experienced MSK sonographers
	Real time imaging	Narrow field of view
	Provocative patient maneuvers	Targeted, focused exam lacking the anatomic overview of other modalities
	Guidance for numerous procedures	
Computed tomography (CT)	Very wide availability	Ionizing radiation
	Rapid image acquisition	Potential adverse reactions if IV contrast needed
	Largely "turnkey" and operator-independent	Insensitive for bone marrow abnormalities
	Guidance for numerous procedures	
	Excellent assessment of cortical bone (including erosion and destruction by tumor, infection, or inflammatory arthritis)	
Magnetic resonance imaging (MRI)	No ionizing radiation	Expensive
	Outstanding soft tissue contrast resolution	Comparative less availability
	Superb bone marrow evaluation	Numerous contraindications
		Long imaging time, claustrophobia
		Nephrogenic systemic fibrosis (NSF) risk from gadolinium-based contrast agents (GBCAs)
		Relatively limited assessment of cortical bone (vs. CT)
Nuclear medicine (NM)	Less expensive than MRI	Ionizing radiation
Bone scintigraphy (BS)	Very large field of view (whole body assessment routinely performed)	Specificity limited (recently improved by adding CT)
Labeled leukocyte study (WBC)	Allows evaluation for multifocal disease	Relatively limited in precise anatomic localization of pathology (better with SPECT, recent improvement with CT)
	Low resolution	
	Sensitivity high	Long study length (especially labeled WBC: imaging performed 2–4, 24, and possibly also 48 h postinjection)
	Negative predictive value (NPV) high	

(continued)

Table 1.2 (continued)

Imaging modality	Advantages	Disadvantages and limitations
Nuclear medicine (NM) FDG-PET	Very large field of view (whole body assessment routinely performed)	Ionizing radiation
	Allows evaluation for multifocal disease	Limited availability
	Sensitivity high	High cost
	Negative predictive value (NPV) high	Insurance reimbursement roadblocks
		Comparatively limited in precise anatomic localization of pathology (recently improved by addition of CT to create hybrid PET (PET/CT))

pregnant women. In appropriate well-trained, experienced hands, sonography excels in a number of applications. One of its main strengths is the ability to distinguish cystic from solid lesions. In addition, application of Doppler US enables visualization of a lesion's vascularity. US permits real time imaging, which allows for provocative maneuvers to detect pathology that is not well shown on static imaging studies. Examples of provocative maneuvers using dynamic real time US include compression of the gallbladder (sonographic Murphy sign) in evaluation of cholecystitis, elbow flexion to elicit ulnar nerve subluxation from the cubital tunnel, hip flexion to show snapping of the iliopsoas tendon in the groin, or compression of vessels to augment flow and show the absence of thrombus. US can also be used to guide interventional procedures including biopsy, e.g., liver or mass biopsy, and therapy such as injection of tendon sheaths, joints, bursae, and peritendinous soft tissues, e.g., the common extensor tendon origin at the lateral epicondyle of the elbow (tennis elbow).

US is operator-dependent. This means that specifically trained imagers are needed for this type of examination. US transducers have a narrow field of view, and so with today's scanning methods, it is possible to overlook pathology. Accordingly, US tends to be most successful when used to answer a specific clinical question with a focused examination of a limited anatomic region. Despite these limitations, the role of US continues to expand, especially the use of ultrasound-guided procedures.

Computed Tomography

CT technology has improved vastly since its introduction. It is now possible to image any part of the body with high spatial and moderate contrast resolution. Similar to CR, CT is readily and near universally available, even in rural locations, "after hours" and on weekends when other modalities are not available. As a result, CT has become the workhorse of diagnostic imaging. With newer scanners, it is possible to

image large tissue volumes rapidly and if necessary repeatedly. This means that CT scans, either without or with the use of oral and/or intravenous contrast, can be configured to answer many clinical questions in every organ system. In fact, CT angiography has largely replaced conventional angiography for routine diagnosis.

When MRI is contraindicated or unavailable, CT often serves as a backup examination. In these cases, it is important to understand the differences in sensitivity and specificity between the two modalities for the clinical question being addressed. CT has better spatial resolution than MRI and is more sensitive at identifying calcium, but it has much lower contrast resolution compared with MRI, making its differentiation of structures poor in some parts of the body. These differences determine the value of attempting a CT as an alternative to MRI. This information will be covered further in the chapters on imaging of specific organ systems.

The main disadvantage of CT is its use of ionizing radiation. CT gives a higher dose of radiation to the patient than routine CR. Several studies have suggested that liberal use of CT will increase the incidence of neoplasms years on. In fact, today, dose levels with each scan are reported and recorded. So, while CT is an excellent diagnostic tool, the danger of high accumulated doses of radiation with this modality should temper its use. This is particularly true in the pediatric population where US should be employed whenever possible to avoid the radiation exposure from CT.

Magnetic Resonance Imaging

Although comparatively expensive, MRI is a commonly performed examination, particularly in neurologic, MSK, and to some extent cardiothoracic and abdominal disease. MRI has superior contrast resolution to other modalities and so is able to depict soft tissue structures that cannot be resolved by other imaging techniques.

As with CT, contrast agents are available for MR. These agents, primarily gadolinium-based, behave similarly to the iodinated contrast agents used for CT and fluoroscopic imaging. They have specific indications that will be discussed in each organ system chapter as appropriate. Other contrast agents are becoming available for specific use, for example, iron-based agents for the liver that are designed specifically for uptake by Kupffer cells. These are not yet widely available and have issues with toxicity.

MRI can accommodate a larger field of view than US, but it is important to understand that as the field of view increases, spatial resolution suffers. Spatial resolution is limited with MRI, and so the larger the field of view, the coarser the image detail obtained. In general, if a large area of the body needs to be imaged, or if there is suspicion for multifocal disease that requires imaging more than one anatomic location, nuclear imaging should be strongly considered in place of MRI. These scans, though often nonspecific, can include nearly the entire body in their field of view, something that is impractical with MRI. On the other hand, in some circumstances wide field of view MRI is useful, for example when surveying the skeleton for multiple myeloma.

Table 1.3 Study contrast media utilization[a] and contraindications in MRI/CT

Imaging modality	Indications (dosing route)	Contraindications (CI): absolute (A), relative (R)
MRI	Paraspinal, epidural abscess (IV)	Endocranial vascular clips (some) (A)
	Soft tissue abscess (IV)	Intra-aortic balloon pump (A)
	Intraosseous abscess (IV)	LVAD, RVAD (A)
	Bone sequestrum (IV)	Pulmonary artery catheter (A)
	Suspected early RA (IV)	Cardiac pacemaker (R)
	Synovitis, tenosynovitis (IV)	Implantable cardiovertor-defibrillator (R)
	Myositis (IV)	Capsule endoscopy device-Pillcam (A)
	Soft tissue mass (IV)	Hemostatic vascular clips (some) (A) Cochlear implants (R)
	Soft tissue necrosis, myonecrosis (IV)	Eye metallic foreign body (R)
	Osteonecrosis (IV)	Insulin pump (R)
	Direct MR arthrography (IArt)	GFR <15 mL/min (R)
	Indirect MR arthrography (IV)	ESRD on chronic dialysis (R)
	Vascular enhancement (IV)	GBCA use during pregnancy (R)
CT	Paraspinal, epidural abscess (IV)	Previous severe adverse reaction (e.g., profound vasovagal reaction, seizure, moderate and severe bronchospasm, laryngeal edema, severe hypotension, sudden cardiac arrest, cardiopulmonary complete collapse, and organ and system-specific adverse events)
	Soft tissue abscess (IV)	Acute kidney injury (AKI)
	Soft tissue mass (IV)	Oliguric dialysis patient (e.g., not ESRD anuric dialysis patient)
	Soft tissue necrosis, myonecrosis (IV)	
	CT arthrography (IAart)	
	Vascular enhancement (IV and IA)	

[a]Contrast agents: *MRI* gadolinium-based contrast agent (GBCA), *CT* iodinated contrast media; Administration: *IV* intravenous, *IA* intra-arterial, *IArt* intra-articular

There are a number of relative and absolute contraindications to the use of MRI. Because MRI uses strong magnetic fields, it can be dangerous to put patients with ferromagnetic devices and implants into a scanner (Table 1.3). First, depending on the device, its location in the body, and the duration that it's been implanted, the magnetic field may cause it to torque or dislodge. Second, depending on the configuration of the implanted device, the MR unit may cause it to generate microwaves and local tissue heating. Finally, the MR unit's magnetic field can trigger some pacemakers to go into test mode.

The list of contraindicated materials is a fluid one and a constant work in progress, with new additions (and removals) being made on a frequent basis. Many

newer devices and implants are specifically designed to be MR compatible. Manufacturers usually provide patients with MR compatibility documentation to carry with them. Resources on the web, e.g., www.mrisafety.com maintain online up-to-date databases on the MR safety of medical devices. In order to use these, however, the patient must be able to provide relevant information regarding their device such as the manufacturer, model number, and date of manufacture. Finally, many radiologists experienced with MRI can help determine which types of devices are MR compatible.

Nuclear Medicine

NM studies had been designed to evaluate specific problems in every organ system whether the endocrine, e.g., thyroid scans, the MSK system, bone scans for osseous metastases or in the GI system, GI bleeding studies, and HIDA scans for gallbladder disease. Most nuclear medicine scans, though nonspecific, have the advantage of being comparatively sensitive and of providing physiologic information regarding target pathology. Furthermore, the recent addition of positron emission scanning (PET) alone and in combination with CT (PET/CT) has moved nuclear medicine into the fore of soft tissue tumor diagnosis and staging. This technique allows subtle areas of tumor to be discovered, diagnosed, staged, and so appropriately treated. PET/CT also has provided new tools for assessment of tissue viability, particularly in cardiac applications.

Contrast Media

Overview

Over the years, various types of contrast media have been used in attempts to improve the quality of imaging. These have provided significant additive value to the imaging modalities where they have been utilized. As a result, today contrast media are used on a routine, daily basis, especially iodinated contrast media for CT and radiography and gadolinium-based contrast agents (GBCAs) with MRI.

The majority of indications for use of intravenous (IV) contrast agents, regardless of whether it is iodinated contrast media or a GBCA, involve use of cross-sectional imaging for infectious, inflammatory, ischemic, and neoplastic pathology. For example, IV contrast material aids in the detection and delineation of fluid collections, regardless of their anatomic location. It also facilitates assessment of osseous and soft tissue viability, e.g., showing areas of necrosis in soft tissue and bone neoplasms and bony sequestra in chronic osteomyelitis. Inflammatory processes such as a variety of types of myositis, tenosynovitis, and synovitis are also

typically better evaluated with IV contrast media. In addition, both iodinated and gadolinium (Gd)-based contrast agents very frequently enable determination of whether a soft tissue mass is cystic or solid in nature. The indications for utilization of IV contrast media are given in Table 1.3.

Contrast is also used intra-arterially (IA) for direct evaluation of the vessels. This is usually done with a catheter placed selectively into the vessel to be imaged. For unknown reasons, allergic contrast reactions to IA injected media are much less common than for IV injected contrast. Even so, because of the greater morbidity of direct contrast arteriography and the sophistication of current CT technology, IV contrast and CTA are more commonly used today.

Contrast media is commonly used intra-articularly as well, allowing the radiologist to actively distend the joint and thereby improve separation of intracapsular structures and enhance image resolution (Table 1.3). Intra-articular contrast injection is much more commonly performed with GBCA and MRI than iodinated contrast and CT, because of the inherent superiority of MRI in soft tissue contrast resolution. Regardless, as with IA injections, allergic reactions with intra-articular contrast are rare.

Contrast is also used intrathecally for myelography. Since the advent of MRI, the indications for myelogram have fallen markedly, but they are still performed in patients where there is a contraindication to MRI or there is adjacent metallic hardware that will induce obscuring MRI artifact.

Contrast agents are not without risk. Adverse side effects from the utilization of contrast media vary from relatively common, minor physiological disturbances that are almost always self-limited to rare, severe life-threatening anaphylactic reactions. In addition, iodinated contrast agents are nephrotoxic and are contraindicated in patients with renal failure as they may worsen renal function precipitously. GBCA are associated with nephrogenic systemic fibrosis (NSF) in patient with poor renal function. Therefore, prior to giving a patient contrast, their renal status should be assessed. Risks of a reaction should be considered when making decisions regarding patient management [1].

Preceding the actual imaging of a patient, the radiologist in conjunction with the ordering physician should address a few preliminary considerations for any given patient. Specifically, the radiologist in particular should make best efforts to determine if there is an appropriate indication for the requested study, identify relative contraindications and pertinent risk factors that may increase the likelihood of an adverse reaction to contrast administration, and possess sufficient knowledge of alternative imaging modalities [1].

Risk Factors Associated with Iodinated Contrast Media

Risk factors for adverse reactions to IV iodinated contrast material include prior reaction, known allergy (history of prior allergic-type reaction particularly if moderate to severe in degree), asthma, renal insufficiency, and cardiovascular

disease (if the patient has congestive heart failure symptoms or angina, severe aortic stenosis, severe cardiomyopathy, or primary pulmonary hypertension) [1]. There are a number of miscellaneous risk factors. One of these is multiple myeloma, which is known to cause irreversible renal failure from renal tubular protein precipitation and aggregation when high-osmolality contrast media (HOCM) is used in these patients. Other potential miscellaneous risk factors include β-adrenergic blockers, which are associated with more frequent and more severe adverse events, and pheochromocytoma, where an increase in serum catecholamine levels may be seen after IV injection of HOCM resulting in a hypertensive crisis [1].

Premedication

Patients who are known to be at higher risk for an acute allergic-type contrast reaction and for whom a scan is needed should be considered for premedication prior to a scan. Many adverse reactions are associated with direct release of histamine and other mediators from circulating basophils and eosinophils [1]. Studies have shown that IV steroids suppress whole blood histamine and show a reduction in circulating basophils and eosinophils [2].

This observation provides a scientific basis for the use of IV steroids in "at risk" patients during emergency situations. Corticosteroids have been shown to have a prophylactic effect for adverse reactions to contrast media in certain circumstances. Some corticosteroid preventative effect may be obtained as soon as 1 h after IV injection of corticosteroids, but experimental data support a much better prophylactic effect if the examination is not performed until at least 4–6 h after giving premedication [3–5]. No clinical studies have demonstrated unequivocally prevention of contrast reactions using short-term IV corticosteroid premedication. If the time frame available for utilizing corticosteroids is too short and the risks of a major reaction judged to be small, some physicians will forgo them and administer only an antihistamine before contrast use [4].

Whether in the emergent or elective setting, it is most important to target premedication to those who, in the past, have had moderately severe or severe reactions that required treatment. Unfortunately, studies thus far have shown that the majority of patients who benefit from premedication are those who have had minor contrast reactions that typically require no or minimal medical intervention [5]. To date, randomized controlled clinical trials have not demonstrated premedication protection against severe life-threatening adverse reactions [3, 6, 7].

Oral administration of steroids is preferable to IV administration, and prednisone and methylprednisolone are equally effective. Regardless of the route of corticosteroid administration, ideally the steroids should be given at least 6 h prior to the injection of contrast media. It is unclear if steroid administration within 3 h of contrast media administration reduces adverse reactions. Some recommended and commonly used dosing schedules for premedication in either the elective or

Elective Premedication

Two frequently used regiments are:

1. Prednisone – 50 mg by mouth at 13 hours, 7 hours, and 1 hour before contrast media injection, plus

   Diphenhydramine (Benadryl®) – 50 mg intravenously, intramuscularly, or by mouth 1 hour before contrast medium.

   or

2. Methylprednisolone (Medrol®) – 32 mg by mouth 12 hours and 2 hours before contrast media injection. An anti-histamine (as in option 1) can also be added to this regimen injection.

   If the patient is unable to take oral medication, 200 mg of hydrocortisone intravenously may be substituted for oral prednisone in the Greenberger protocol.

Emergency Premedication (In Decreasing Order of Desirability)

1. Methylpredniolone sodium succinate (Solu-Medrol®) 40 mg or hydrocortisone sodium succinate (Solu-Cortef®) 200 mg intravenously every 4 hours (q4h) until contrast study required plus diphenhydramine 50 mg IV 1 hour prior to contrast injection.

2. Dexamethasone sodium sulfate (Decadron®) 7.5 mg or betamethasone 6.0 mg intravenously q4h until contrast study must be done in patent with known allergy to methylpred-nisolone, aspirin, or non-steroidal anti-inflammatory drugs, especially if asthmatic. Also diphenhydramine 50 mg IV 1 hour prior to contrast injection.

3. Omit steroids entirely and give diphenhydramine 50 mg IV.

   Note: IV steroids have not been shown to be effective when administered less than 4 to 6 hours prior to contrast injection.

Fig. 1.1 Recommended premedication regimens to reduce frequency and/or severity of reactions to iodinated contrast media (From: [1] Manual on Contrast Media, Version 8. Reston, VA: American College of Radiology; 2012)

emergent setting are included below (Fig. 1.1) [1]. Further, oral or intravenous administration of an H-1 antihistamine, e.g., diphenhydramine, either alone or as a supplement to corticosteroids may reduce the frequency of urticaria, angioedema, and respiratory symptoms [1].

Breakthrough Reactions

Repeat contrast reactions in premedicated patients are termed breakthrough reactions. Breakthrough reactions most often are similar to the index reaction. Patients with a previous mild contrast reaction have an extremely low risk of developing a severe breakthrough reaction. The majority of low-osmolality contrast material

(LOCM) injections in premedicated patients who had prior breakthrough reactions will not result in a repeat breakthrough reaction [8, 9]. On the other hand, although there is a decrease in the overall adverse events after steroid premedication prior to contrast injection, studies have shown no decrease in the incidence of repeat severe adverse events [10].

Adverse Events Following Iodinated Contrast Media Administration

The frequency of adverse events after administration of iodinated contrast media can be decreased by utilization of nonionic LOCM [11–13]. Several studies have reported overall adverse reaction rates or allergic-like reaction rates ranging from 0.18 to 0.7 % [1]. HOCM use historically has been associated with a much higher rate of acute adverse reactions of 5–15 % [1], but HOCM is not used commonly anymore.

Acute adverse events after iodinated contrast media use can be subdivided into several categories, allergic-like or physiologic, and these are classified further as mild, moderate, or severe (Fig. 1.2) [1]. Other reactions are organ or system-specific reactions (Fig. 1.3) [1].

Allergic-like reactions are clinically identical to an anaphylactic reaction to any other drug or allergen [12–14]. Physiologic reactions include commonly occurring but usually mild and self-limited vasovagal reactions like hypotension with bradycardia [13], as well as rare cardiovascular events such as arrhythmias, impaired myocardial contractility [13–15], and both cardiogenic and noncardiogenic pulmonary edema [16].

Mild adverse reactions are frequently nonallergic-like physiologic responses (e.g., nausea, vomiting, and a feeling of warmth). Whether allergic-like or nonallergic-like, these mild effects usually do not require medical treatment, but they do have the potential to evolve into a more severe reaction and so must be monitored [1]. Moderate adverse events may also be allergic-like, e.g., severe urticaria/erythema, bronchospasm, moderate tongue/facial swelling, transient hypotension with tachycardia, or nonallergic-like, e.g., significant vasovagal reaction. In most instances, these adverse reactions are not immediately life-threatening. Nonetheless, they often require medical treatment. As with mild adverse reactions, events in the moderate group have the potential to worsen, in the latter case resulting in significant morbidity or even mortality [1]. Severe adverse events are usually allergic-like, but also may be physiologic. Acute adverse advents that fall under the category of serious reactions occur in only 0.01–0.02 % of imaging studies where LOCM is used [17]. Although these allergic reactions are quite rare, they may be life-threatening, and the majority of patients require treatment. Severe reactions include altered mental status, respiratory distress due to severe bronchospasm or laryngeal edema, severe hypotension, and sudden cardiac arrest. Complete

Categories of Reactions

Classification of Severity and Manifestations of Adverse Reactions to Contrast Media

Mild

Signs and symptoms appear self-limited without evidence of progression (e.g., limited urticaria with mild pruritis, transient nausea, one episode of emesis) and include:

- Nausea, vomiting
- Cough
- Warmth
- Headache
- Dizziness
- Shaking
- Altered taste
- Itching
- Pallor
- Flushing
- Chills
- Sweats
- Rash, hives
- Nasal stuffiness
- Swelling: eyes, face
- Anxiety

Treatment: Requires observation to confirm resolution and/or lack of progression but usually no treatment. Patient reassurance is usually helpful.

Moderate

Signs and symptoms are more pronounced. Moderate degree of clinically evident focal or systemic signs or symptoms, including:

- Tachycardia/bradycardia
- Hypertension
- Generalized or diffues erythema
- Dyspnea
- Bronchospasm, wheezing
- Laryngeal edema
- Mild hypotension

Treatment: Clinical findings in moderate reactions frequently require prompt treatment. These situtaions require close, careful observation for possible progression to a life-threatening event.

Severe

Signs and symptoms are often life-threatening, including:

- Laryngeal edema (severe or rapdidly progressing)
- Profound hypotension
- Clinically manifest arrhythmias
- Convulsions
- Unresponsiveness
- Cardiopulmonary arrest

Treatment: Requires prompt recognition and aggressive treatment, manifestations and treatment frequently require hospitalization.

Note: The above classifications (mild, moderate, severe) do not attempts to distiguish between allergic-like and non-allergic like reactions. Rather, they encompass the specrum of adverse events that can be seen following the intravascular injection of contast media.

Fig. 1.2 Categories of reactions to contrast media administration (From: [1] Manual on Contrast Media, Version 8. Reston, VA: American College of Radiology; 2012)

cardiopulmonary collapse is extremely rare. Less frequent than their allergic-like counterparts, severe nonallergic-like adverse events are also possible and usually necessitate medical management other than epinephrine. These include prominent vasovagal reactions, pulmonary edema, and seizures [1].

Organ and System-Specific Adverse Effects from the Administration of Iodine-Based or Gadolinium-Based Contrast Agents

Individual organs can manifest isolated adverse effects caused by the administration of contrast media.

Adrenal Glands
- Hypertension (in patients with pheochromocytoma after intra-arterial injection)

Brain
- Headache
- Confusion
- Dizziness
- Seizure
- Rigors
- Lost or diminished consciousness
- Lost or diminished vision

Gastrointestinal Tract
- Nausea
- Vomiting
- Diarrhea
- Intestinal cramping

Heart
- Hypotension
- Dysrhythmia (asystole, ventricular fibrillation/ventricular tachycardia)
- Pulseless electrical activity (PEA)
- Acute congestive heart failure

Kidney
- Oliguria
- Hypertension
- Contrast-induced nephropathy (CIN)

Pancreas
- Swelling / pancreatitis

Respiratory System
- Laryngeal edema
- Bronchospasm
- Pulmonary edema

Salivary Glands
- Swelling / parotitis

Skin and Soft Tissues
- Pain
- Edema
- Flushing
- Erythema
- Urticaria
- Pruritus
- Compartment syndrome (from extravasation)
- Nephrogenic Systemic Fibrosis (NSF)

Thyroid
- Exacerbation of thyrotoxicosis

Vascular System
- Hemorrhage (due to direct vascular trauma from contrast injection or from the reduction in clotting ability
- Thrombophlebitis

Fig. 1.3 Organ and system-specific adverse events after administration of iodine-based or gadolinium-based contrast media (From: [1] Manual on Contrast Media, Version 8. Reston, VA: American College of Radiology; 2012)

Organ and system-specific adverse reactions refer to adverse effects on a more isolated basis. Neurologic, cardiovascular, and renal abnormalities account for the majority of the adverse events in this group. Contrast-induced nephrotoxicity (CIN) is the most significant organ-specific adverse effect and is discussed in more detail below [1].

Risk factors for acute adverse events following contrast administration can be identified for allergic-like reactions. Prior allergic-like reaction is the biggest risk factor [11, 12], with a reported incidence of recurrent adverse event as high as 35 % [18]. Patients with asthma or a history of atopia also are at increased risk for adverse reaction, although the risk is not as high as in those with history of prior allergic-like event [13–15].

Non-Acute, Delayed Adverse Reactions

Nearly all life-threatening iodinated contrast media reactions occur immediately or within the first 20 min after contrast media injection [1]. Notwithstanding, non-acute adverse reactions to iodinated contrast media may arise between 3 h and 2 days, but have been seen as early as 30 min or as late as 7 days after contrast administration [18, 19]. These delayed adverse events may be allergic-like or nonallergic-like, but they are most commonly allergic-like and cutaneous in nature, presenting as urticaria and/or a persistent rash. The incidence of these events is not rare with reports ranging from 0.5 to 14 % [19, 20]. Most cases are self-limited and require minimal if any treatment other than symptomatic support [1]. Severe delayed adverse events are extraordinarily rare but may occur. The recurrence rate of delayed contrast reactions upon reexposure to contrast material is not known, but anecdotally may be higher than 25 % [21]. It is not clear if corticosteroid premedication is indicated before a subsequent contrast-enhanced study in patients with a history of delayed allergic-like contrast reaction [1].

Contrast-Induced Nephrotoxicity

CIN is a sudden deterioration in renal function after recent intravascular administration of iodinated contrast medium in the absence of another nephrotoxic event [22]. CIN is either exceedingly rare or does not occur with use of GBCAs [1]. The pathophysiology of CIN and associated acute kidney injury is not well understood. Fortunately, CIN usually follows a course of transient asymptomatic elevation in serum creatinine, beginning to rise within 1 day, peaking within 4 days, and typically returning to baseline within 7–10 days. Chronic renal dysfunction is unusual unless other risk factors are present [1].

The most unequivocal, clear risk of developing CIN is preexisting renal insufficiency [23]. Numerous other proposed risk factors, including diabetes mellitus, hypertension, and multiple doses of iodinated contrast over a short time period (e.g., <24 h), have not been convincingly confirmed in the literature. Numerous papers have found the incidence of CIN is less with IV than IA iodinated contrast media.

At the present time, the practice guideline of the American College of Radiology (ACR) for the use of IV iodinated contrast material with regard to the potential risk of CIN is that there is insufficient data to set a specific recommended threshold level for serum creatinine above which iodinated contrast should not be given. Most institutions withhold contrast when the creatinine is greater than or equal to 2.0 mg/dL [1]. Many use lower levels as the cut off.

Patients older than age 60, those with hypertension, diabetes mellitus, and known renal risk factors, including a history of a single kidney, renal transplant, kidney surgery, renal cancer, and dialysis, should be routinely screened with a serum creatinine level before receiving iodinated contrast [24, 25]. Use of less nephrotoxic

LOCM [26] and adequate patient hydration prior to the study [27] are standard practices in an attempt to limit the possibility of CIN. Several pharmacological agents, including IV sodium bicarbonate, *N*-acetylcysteine, diuretics, theophylline, and fenoldopam, thus far have been unconvincing as far as their efficacy with regard to preventing CIN [1].

Metformin

The anti-hyperglycemic agent, Metformin, has been associated with a rare but life-threatening complication in patients who receive intravascular iodinated contrast. The kidneys eliminate this anti-hyperglycemic agent, excreting approximately 90 % of a dose within the first 24 h. Instances have been reported in which patients taking metformin develop lactic acidosis after receiving iodinated contrast media [1]. The apparent cause is that contrast-induced decline in renal function leads to elevated Metformin levels which in turn cause increased production of lactic acid by the GI tract. Although this complication is estimated to occur at a rate of no more than 0.1 cases per 1,000 patient years, when Metformin-associated lactic acidosis occurs, mortality is approximately 50 % [1].

In almost all reported cases of this serious adverse reaction, lactic acidosis likely developed because associated other contraindications and comorbidities for the drug were overlooked, i.e., renal or cardiovascular disease, but also decreased lactate metabolism states from hepatic dysfunction and alcohol abuse, as well as increased anaerobic metabolism resulting from sepsis or severe infection. In properly selected patients, there have been no documented cases of Metformin-associated lactic acidosis [1].

The ACR recommends that patients taking Metformin who are scheduled to receive iodinated contrast media be stratified into three groups. This stratification of patients should be done on the basis of pre-examination renal function, and known comorbidities associated with decreased lactate metabolism or increased anaerobic metabolism. Management of the individual patient will vary depending on their classification category, including possible Metformin discontinuation, continued assessment of renal function following the imaging study, and the timing of the reinstitution of Metformin [1].

Adverse Events After Gadolinium-Based Contrast Agent Administration

The incidence of acute adverse events after administration of a routine IV dose gadolinium chelate ranges from 0.07 to 2.4 %. The vast majority of these reactions is mild and resembles adverse reactions from use of iodinated contrast media. Severe, life-threatening allergic or nonallergic anaphylactic reactions are extremely

rare with an incidence of 0.001–0.01 %. Fatal reactions to gadolinium chelate agents, although possible, are exceedingly rare [1].

As with iodinated contrast media, a history of prior adverse reaction to GBCA places the patient at much greater risk (approximately 8×) for a repeat adverse advent. Similarly, patients with asthma and other allergies have an increased incidence of allergic-like adverse events with GBCA, as high as 3.7 % [1].

When used at approved dosages, there is no significant evidence to suggest that GBCA is nephrotoxic. Instead, use of a GBCA in patients with advanced renal dysfunction (those with ESRD and a creatinine clearance of <15 cm^3/min, but also others with a creatanine clearance of 15–30 cm^3/min) places the patient at significant risk for the development of NSF. GBCA crosses the blood-placenta barrier into the fetal blood stream, and it may accumulate in amniotic fluid, thus making its use in pregnant patients a relative contraindication [1].

Nephrogenic Systemic Fibrosis

The first cases of NSF were diagnosed in 1997, and the first published report of 14 cases appeared back in 2000 [28]. Despite this, NSF only recently has received considerable attention in the medical community, largely because of identification of a possible link with GBCA agents that have been widely used in MRI for the past 20 years. In 2006, several groups made the observation of a strong association between GBCA administration and development of NSF in patients with advanced renal disease, and it is now widely accepted that exposure to GBCA is a prerequisite to develop NSF.

The disorder was initially termed nephrogenic fibrosing dermopathy given the prominence of its skin manifestations, which include thick, hard skin starting in the extremities, sometimes extending to the torso, and resembling that of progressive systemic sclerosis [29]. After multiple autopsy case reports on patients with the disease that described myocardial, pericardial, and pleural fibrosis, along with nerve and skeletal muscle involvement, nephrogenic fibrosing dermopathy was renamed NSF to emphasize the non-dermatological features of the disorder [30]. Patients afflicted by NSF not only have wooden, unpinchable skin; they also may have scleral plaques, joint contractures, muscle weakness, pruritus, and sharp pain. Arriving at a confident diagnosis of NSF in a given individual is a complex undertaking that relies on the expertise of specialist physicians, clinical history and physical examination, and tissue sampling. More specifically, the diagnosis of NSF involves physical exam of the patient by a seasoned dermatologist or rheumatologist, and histopathologic assessment of skin biopsy tissue by an experienced dermatopathologist [31, 32].

The incidence of NSF in much of the literature varies from 3 to 7 % in patients receiving Omniscan (gadodiamide) [31], the GBCA administered in a very large percentage of reported NSF cases. One study reported an incidence of NSF of 18 % for patients in the highest risk group (GFR <15 mL/min) [33]. About 5 % of patients

with NSF are afflicted by the fulminant subtype of the disorder. These patients experience rapid progression of disease including accelerated loss of mobility and severe pain [32]. In those cases where NSF is fatal, visceral involvement is the most common cause of death, especially cardiovascular events [34].

In 2008, Knopp et al. observed that all documented cases of NSF to date had acute or chronic renal insufficiency (GFR <30 mL/min); were related to acute renal insufficiency in hepatorenal syndrome; or arose perioperatively in liver transplantation patients [31]. Most cases of biopsy-proven NSF reported in the peer-reviewed literature are associated with ESRD (GFR <15 mL/min) (85 %), Omniscan (gadodiamide) GBCA, exposure to a single high dose, or more commonly multiple doses of contrast, within a 6 month time frame, the last exposure to contrast within 6 months, and current or previous dialysis (62 %) [31]. A high total cumulative lifetime dose of GBCA increases the risk of NSF. There has been only one published case report of a patient with GFR >30 mL/min acquiring NSF [35] (Table 1.4).

Cases of NSF can be categorized as confounded or unconfounded. Confounded cases are those in which the patient has a history of having received more than one type of GBCA prior to onset of NSF, while in unconfounded cases the patient was exposed to only a single GBCA. In a meta-analysis of the literature published in 2008, out of 168 unconfounded cases of NSF, the overwhelming majority involved Omniscan (gadodiamide) (93 %), distantly followed by Magnevist (gadopentetate dimeglumine) (5 %) and then Optimark (gadoversetamide) (2 %) [36]. Other brands of GBCAs have been associated with few, if any, confirmed cases of NSF (Fig. 1.4) [1]. Thus, the precise relationship between NSF and different formulations of GBCAs is controversial and incompletely understood.

Since most patients, including those with ESRD, do not develop NSF, other possible triggers, cotriggers, or predisposing conditions have been suggested, such as vascular surgery, hypercoagulability or thrombotic events, high-dose erythropoietin administration, immunosuppression, infection, proinflammatory state, metabolic acidosis, and elevated serum levels of iron, calcium, and phosphorus [1, 31, 32] (Table 1.4). To date, there is no clear evidence that any of these factors play a role in the development of NSF.

It is now widely accepted that GBCA exposure is a prerequisite for the development of NSF [1]. The exact mechanism by which GBCA exerts its effect in NSF is unknown, or at least not well understood. The most favored theory is that the gadolinium (Gd) ion dissociates from its chelate and then binds other anions such as phosphate producing an insoluble precipitate that remains in the skin and other tissues for weeks, months, or even years [1, 32], thus inciting a fibrotic reaction.

Since the medical community does not know why only a minority of patients at risk develop NSF, caution should be exercised when administering GBCA in patients with advanced renal failure. Assessment of the risks and benefits of GBCA administration should be performed for each patient via close consultation between radiologist and clinician and GBCA administered only to patients where the information provided by its use is both essential to patient care and unable to be obtained by other means [31]. If a decision is made to utilize GBCA, the imaging study should be monitored by the radiologist. If the initial non-contrast images

Table 1.4 Nephrogenic systemic fibrosis (NSF)

Signs and symptoms	Epidemiology	Pathophysiology	Triggers, cotriggers, and predisposing conditions	Notes
Thick, hard, wooden skin	ESRD (GFR <15 mL/min): 85 % of patients with NSF	Exact mechanism of NSF development unknown or poorly understood	Vascular surgery	Close consultation between radiologist and clinician essential to appropriate risk-benefit assessment
Pruritus	Symptom onset within days to 6 months of last exposure	Most widely favored theory:	Hypercoagulability	Perform contrast study only if the desired information is essential and cannot be obtained by other means
Lungs, heart, esophagus, and skeletal muscles Myocardial, pericardial, and pleural fibrosis	Exposure to single high dose or multiple doses within 6 month time frame	Gadolinium (Gd) ion dissociates from its chelate, free Gd binds other anions, and resultant insoluble precipitate deposits in soft tissues	High dose erythropoietin	Radiologist should monitor study and determine if non-contrast images are diagnostically adequate (obviating need for GBCA)
Joint contracture	High total cumulative lifetime dose of GBCA increases risk	GBCA able to cross the blood-placenta barrier into the fetus, and likely accumulates in amniotic fluid (relative contraindication)	Immunosuppression	Coordinate for hemodialysis (~2 and possibly 24 h after MRI) to enhance GBCA elimination
Muscle weakness Death (usually due to visceral involvement)	Dialysis: current or past NSF incidence: ~3–7 % Rapidly progressive NSF: <5 % Most common agent used in unconfounded cases of NSF: Omniscan		Infection Metabolic acidosis High Fe, Ca^{2+}, P levels	

Group I: Agents associated with the greatest number of NSF cases:

Gadodiamide (Omniscan® – GE Healthcare)
Gadopentetate dimeglumine (Magnevist® – Bayer HealthCare Pharmaceuticals)
Gadoversetamide (OptiMARK®–Covidien)

Group II: Agents associated with few, if any, unconfounded cases of NSF:

Gadobenate dimeglumine (MultiHance® – Bracco Diagnostics)
Gadoteridol (ProHance® – Bracco Diagnostics)
Gadoteric acid (Dotarem® – Guerbet – as of this writing not FDA-approved for use in the U.S.)
Gadobutrol (Gadavist® – Bayer HealthCare Pharmaceuticals)

Group III: Agents which have only recently appeared on the market in th US:

Gadofosvest (Ablavar® – Lantheus Medical Imaging)
Gadoxetic acid (Eovist® – Bayer HealthCare Pharmaceuticals)

There is limited data for Group III agents, although, to date, few, if any, unconfounded cases of NSF have been reported.

Fig. 1.4 Association between various Gadolinium-based contrast agent (GBCA) and cases of NSF (From: [1] Manual on Contrast Media, Version 8. Reston, VA: American College of Radiology; 2012)

are diagnostically adequate, the radiologist can cancel the planned utilization of Gd contrast [31].

The radiologist and clinician can also coordinate post-MRI hemodialysis for patients following a study in which GBCA is administered. Dialysis should be performed approximately 2 h and if possible again at 24 h after the MRI to accelerate GBCA elimination. It should be noted, however, that there are currently no data showing that reducing free Gd levels with dialysis decreases the risk of developing NSF [31].

Administration of Iodinated Contrast Media and GBCA in Pregnancy

Studies in the medical literature focusing on fetal effects of iodinated contrast media (both ionic and nonionic) and GBCAs during pregnancy are limited. Potential negative effects on the human embryo and fetus are incompletely understood. Both iodinated contrast agents and gadolinium-based MR contrast media, when administered in doses typically used in clinical practice, cross the human placenta and enter the fetus in measurable quantities [37, 38].

After entering the fetal blood stream, contrast agents are excreted via the urine into the amniotic fluid. This is then swallowed by the fetus [39], a small percentage is absorbed by the GI tact, and the rest returned back to the amniotic fluid. The cycle is then repeated innumerable times. Currently, it is not known how quickly contrast media is cleared from the amniotic fluid.

In-vivo tests in animals have shown no evidence of either mutagenic or teratogenic effects with iodinated low-osmolality contrast media (LOCM). No adequate and well-controlled studies of the teratogenic effects of iodinated contrast agents in pregnant women have been performed. At the current time, there is insufficient evidence to conclude whether or not iodinated contrast media pose a risk to the fetus. Policies and procedures designed to identify pregnant patients prior to exposure to ionizing radiation (e.g., CT) also should be used to assess the medical necessity for administration of iodinated contrast media in these patients.

No well-controlled studies of the teratogenic effects of GBCA in pregnant women have been performed. This class of contrast agent poses more difficulties than iodinated contrast media, largely because less is known about potential fetal toxicities. Gadolinium chelates may accumulate in the amniotic fluid and remain for an indefinite period of time. It is also possible that toxic-free gadolinium can dissociate from its chelate in this environment. Potential toxic effects from exposure to free Gd ions are unknown, as is association between free gadolinium ions and development of NSF in the fetus.

As a result, GBCA should not be used routinely in pregnant patients. The same precautions with the use of GBCA in ESRD patients should be exercised in pregnant women as well. The radiologist should confer with the clinician to be sure that the following criteria are met: (1) the diagnostic information expected to be provided by the MRI cannot be acquired without the use of IV contrast media or by using other imaging modalities, (2) the information needed affects the care of the patient and fetus during the pregnancy, and (3) the referring physician feels that it is not prudent to wait until after parturition to obtain this information.

Administration of Iodinated Contrast Media and GBCA to Breast-Feeding Mothers

Often, patients and/or their physicians have concerns about potential toxicity to the infant caused by contrast media that is excreted into the mother's breast milk. Mothers who are breast-feeding should be given the opportunity to make an informed decision as to whether to continue or temporarily abstain from breast-feeding after receiving intravascularly administered iodinated contrast media or GBCA. The literature on the excretion of iodinated contrast agents (both ionic and nonionic) and GBCA into breast milk and the subsequent gastrointestinal absorption of these agents from breast milk is limited, but sufficient for the ACR to construct a position statement on this topic.

A number of studies have reported that less than 1 % of the maternal dose of iodinated contrast material is excreted into breast milk during the first 24 h. Furthermore, less than 1 % of the contrast medium in the breast milk that the infant ingests is absorbed by its gastrointestinal tract [40–42]. Therefore, the expected dose of contrast media absorbed by an infant from ingested breast milk is less than

0.01 % of the intravascular dose administered to the mother. This amount of contrast material represents less than 1 % of the recommended contrast dose for an infant undergoing an imaging study.

The literature reports that only 0.04 % of the maternal GBCA dose is excreted into the breast milk in the first 24 h. As with iodinated contrast material, less than 1 % of the GBCA in breast milk ingested by the infant is absorbed by its gastrointestinal tract [43, 44]. Thus, the expected dose of GBCA absorbed from ingested breast milk by an infant is less than 0.0004 % of the dose received by the child's mother. This amount of GBCA is 0.04 % of the permitted adult or pediatric (2 years or older) IV dose.

Although free gadolinium is neurotoxic, it is safe for use in most adults and children when complexed to one of a variety of chelates. However, because it is not known how much, if any, of the gadolinium in breast milk is in unchelated form, the infant may be at risk due to direct toxicity from free Gd. Potential risk also includes allergic sensitization or reaction. So far, these are mainly theoretical type concerns.

Because of the very low percentage of iodinated contrast agent or GBCA that is excreted into the breast milk and absorbed by the infant's GI tract, and absence of evidence in the literature that ingestion of this amount of contrast has toxic effects, the ACR position on this issue is that it is safe for the mother and infant to continue breast-feeding after receiving a contrast agent. If the mother remains concerned about contrast media administration having potential ill effects on her infant, a reasonable option is to temporarily abstain from breast-feeding after receiving contrast. Both iodinated contrast agents and gadolinium contrast media have a plasma half-life of approximately 2 h, which results in clearance of nearly 100 % of contrast media from the bloodstream within 24 h. As a result, the mother can discontinue breast-feeding for 24 h, but she must actively express and discard her breast milk during that period.

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