PATIENT SELECTION AND PREPARATION STRATEGIES BEFORE CONTRAST MEDIUM ADMINISTRATION

General Considerations

The approach to patients about to undergo a contrast-enhanced examination has four general goals:

1) to ensure that the administration of contrast is appropriate for the patient and the indication; 2) to balance the likelihood of an adverse event with the benefit of the examination; 3) to promote efficient and accurate diagnosis and treatment; and 4) to be prepared to treat a reaction should one occur (see Tables 2, and 3). Achieving these aims depends on obtaining an appropriate and adequate history for each patient, considering the risks and benefit of using or avoiding contrast medium, preparing the patient appropriately for the examination, having equipment available to treat reactions, and ensuring that personnel with sufficient expertise are available to treat severe reactions.

The history obtained should focus on identification of factors that may indicate either a contraindication to contrast media use or an increased likelihood of an adverse event. Screening questions should include historical elements that will affect decision-making in the patient selection and preparation period.

Risk Factors for Adverse Reactions to Intravenous
Contrast Media Primary Considerations

Allergic-like reactions to modern iodinated and gadolinium-based contrast medium are uncommon (iodinated: 0.6% aggregate [1], 0.04% severe [2]; gadolinium-based: 0.01-0.22% aggregate [3], 0.008% severe) [3, 4]. Risk factors exist that increase the risk of a contrast reaction. These generally increase the likelihood of a reaction by less than one order of magnitude, effectively increasing the risk that an uncommon event will occur, but not guaranteeing a reaction will take place. The following are some examples:

Allergy: Patients who have had a prior allergic-like reaction or unknown-type reaction (i.e., a reaction of unknown manifestation) to contrast medium have an approximately 5-fold increased risk of developing a future allergic-like reaction if exposed to the same class of contrast medium again [3]. A prior allergic-like or unknown type reaction to the same class of contrast medium is considered the greatest risk factor for predicting future adverse events.

In general, patients with unrelated allergies are at a 2- to 3-fold increased risk of an allergic-like contrast reaction, but due to the modest increased risk, restricting contrast medium use or premedicating solely on the basis of unrelated allergies is not recommended. Patients with shellfish or povidone-iodine (e.g., Betadine®) allergies are at no greater risk from iodinated contrast medium than are patients with other allergies (i.e., neither is a significant risk factor) [5,6].

There is no cross-reactivity between different classes of contrast medium. For example, a prior reaction to gadolinium-based contrast medium does not predict a future reaction to iodinated contrast medium, or vice versa, more than any other unrelated allergy.

Asthma: A history of asthma increases the likelihood of an allergic-like contrast reaction [3,7].

Patients with asthma may be more prone to develop bronchospasm. Due to the modest increased risk, restricting contrast medium use or premedicating solely on the basis of a history of asthma is not recommended.

Renal Insufficiency: Screening and selection strategies to mitigate the possible risks of the non-allergic adverse events of contrast-induced nephrotoxicity (CIN) and nephrogenic systemic fibrosis (NSF) can be found in the Chapters on Post-Contrast Acute Kidney Injury and Contrast Induced Nephropathy in Adults and Nephrogenic Systemic Fibrosis.

Cardiac Status: Patients with severe cardiac disease may be at increased risk of a non-allergic cardiac event if an allergic-like or non-allergic contrast reaction occurs. These include symptomatic patients (e.g., patients with angina or congestive heart failure symptoms with minimal exertion) and also patients with severe aortic stenosis, cardiac arrhythmias, primary pulmonary hypertension, or severe but compensated cardiomyopathy. Due to the modest increased risk, restricting contrast medium use or premedicating solely on the basis of a patient's cardiac status is not recommended.

Anxiety: There is some evidence that contrast reactions are more common in anxious patients [8]. Reassuring an anxious patient before contrast medium injection may mitigate the likelihood of a mild contrast reaction.

Other Historical and Pre-Procedure Considerations

Age and Gender: Infants, neonates, children, and the elderly have lower reaction rates than middle-aged patients [1,9] Male patients have lower reaction rates than female patients. Due to the modest increased risk, restricting contrast medium use or premedicating solely on the basis of patient age or gender is not recommended.

Beta-Blockers: Some have suggested that use of beta-blockers lowers the threshold for contrast reactions, increases the severity of contrast reactions, and reduces the responsiveness of treatment with epinephrine [10]. Due to the modest increased risk, restricting contrast medium use or premedicating solely on the basis of beta-blocker use is not recommended. Patients on beta-blocker therapy do not need to discontinue their medication(s) prior to contrast medium administration.

Sickle-Cell Trait/Disease: Some have suggested that contrast medium exposure to patients with sickle cell trait or sickle cell disease might increase the risk of an acute sickle crisis; however, there is no evidence this occurs with modern iodinated or gadolinium-based contrast medium [11]. Therefore, restricting contrast medium use or premedicating solely on the basis of sickle cell trait or sickle cell disease is not recommended.

Pheochromocytoma: There is no evidence that IV administration of modern iodinated or gadolinium-based contrast medium increases the risk of hypertensive crisis in patients with pheochromocytoma [12]. Therefore, restricting contrast medium use or premedicating solely on the basis of a history of pheochromocytoma is not recommended. Direct injection of any type of contrast medium into the adrenal or renal arteries in a patient with pheochromocytoma has not been adequately studied and is of unknown risk.

Myasthenia Gravis: There is a questionable relationship between IV iodinated contrast medium and exacerbations of myasthenic symptoms in patients with myasthenia gravis. While one retrospective study showed no immediate increase in myasthenic symptoms following the administration of iodinated or gadolinium-based contrast medium [13], another that searched for myasthenic exacerbations occurring up to 45 days after a CT scan found that IV non-ionic iodinated contrast medium was associated with an acute (within 1 day of contrast administration) myasthenic exacerbation in approximately 6% of patients (compared to a 1% acute exacerbation rate in patients who had undergone noncontrast CT, p=0.01) [14]. However, that study was retrospective, and the number of events was small. Premedication is not recommended solely on the basis of a history of myasthenia gravis. It is controversial whether iodinated contrast medium should be considered a relative contraindication in patients with myasthenia gravis.

Hyperthyroidism: Patients with a history of hyperthyroidism can develop thyrotoxicosis after exposure to iodinated contrast medium, but this complication is rare [15]. Therefore, restricting contrast medium use or premedicating solely on the basis of a history of hyperthyroidism is not recommended. However, two special situations may affect this:

1. In patients with acute thyroid storm, iodinated contrast medium exposure can potentiate thyrotoxicosis; in such patients, iodinated contrast medium should be avoided. Corticosteroid premedication in this setting is unlikely to be helpful.

2. In patients considering radioactive iodine therapy or in patients undergoing radioactive iodine imaging of the thyroid gland, administration of iodinated contrast medium can interfere with uptake of the treatment and diagnostic dose. If iodinated contrast medium was administered, a washout period is suggested to minimize this interaction. The washout period is ideally 3-4 weeks for patients with hyperthyroidism, and 6 weeks for patients with hypothyroidism [16,17].

Normal Thyroid Function: Iodinated contrast medium does not affect thyroid function test results in patients with a normally functioning thyroid gland [15]. Multiple studies have shown that a single dose of iodinated contrast medium administered to a pregnant mother has no effect on neonatal thyroid function.

Angiography: Iso-osmolality contrast media (IOCM) are associated with the least amount of vasospasm and the least peripheral discomfort for peripheral angiograms [18]. Concomitant use of iodinated contrast medium with certain intra-arterial medications (e.g., papaverine) may lead to precipitation of contrast medium and crystal or thrombus formation. Decisions about the use and timing of such medication are outside the scope of this document.

Pretesting

Intradermal skin testing with contrast media to predict the likelihood of adverse reactions has not been shown to be useful in minimizing reaction risk [19-21].

Corticosteroid Premedication

The purpose of corticosteroid premedication is to mitigate the likelihood of an allergic-like reaction in high- risk patients.

Etiology of Hypersensitivity Contrast Reactions: The etiological mechanism of most immediate hypersensitivity contrast reactions is incompletely understood [22]. It is known, however, that approximately 90% of such adverse reactions are associated with direct release of histamine and other mediators from circulating basophils and eosinophils. It is also generally accepted that most adverse allergic-like reactions are not associated with the presence of increased IgE, and therefore are unlikely to be typical IgE-mediated hypersensitivity reactions. However, some studies show evidence of IgE mediation [19]. No antibodies to IV contrast media have been consistently identified, and according to skin testing and basophil activation, IgE-mediated allergy is uncommon, for example occurring in 4% of patients having anaphylaxis symptoms [20]. This likely explains why patients who have never been exposed to contrast media can experience a severe hypersensitivity reaction on first exposure. Prior sensitization is not required for a contrast reaction to occur.

Pathophysiologic explanations for allergic-like hypersensitivity reactions include activation of mast cells and basophils releasing histamine, activation of the contact and complement systems, conversion of

L-arginine into nitric oxide, activation of the XII clotting system leading to production of bradykinin [11], and development of “pseudoantigens” [23].

The osmolality of the contrast medium as well as the size and complexity of the molecule has potential influence on the likelihood of contrast reactions. Hyperosmolality is associated with stimulation of histamine release from basophils and mast cells. Increase in the size and complexity of the contrast molecule may potentiate the release of histamine [24,25]. There is some evidence to suggest that low-osmolality nonionic monomers produce lower levels of histamine release from basophils compared with high-osmolality ionic monomers, low-osmolality ionic dimers and iso-osmolality nonionic dimers [25]. Low-osmolality monomeric contrast media also are associated with a reduced likelihood of physiologic reactions following intravenous administration (i.e., non-allergic-like; e.g., nausea and vomiting). In general, non-ionic iodinated contrast media are associated with less adverse events than ionic contrast media (iodinated and gadolinium-based) [3,26].

Benefits of Premedication: A randomized trial showed that premedication of average-risk patients prior to high-osmolality iodinated contrast medium administration reduces the likelihood of immediate adverse events of all severity [22]. However, high-osmolality contrast medium is no longer used for intravascular purposes.

Another randomized trial showed that premedication of average-risk patients prior to modern low- osmolality iodinated contrast medium administration reduce the likelihood of mild and aggregate immediate adverse events, but the trial was underpowered to evaluate the effect on moderate and severe reactions [27].

Both of these randomized trials of premedication did not study the effect of premedication in high-risk patients who are usually premedicated today, and neither study was sufficiently powered to evaluate the efficacy of premedication in the prevention of moderate or severe reactions [22,27].

Nonetheless, many experts believe that premedication does reduce the likelihood of a reaction in high- risk patients receiving low-osmolality iodinated contrast medium [28], although the number needed to treat to prevent a reaction is high [29,30]. One study estimated that the number needed to premedicate to prevent one reaction in high-risk patients

was 69 for a reaction of any severity and 569 for a severe reaction [29]. Another study estimated the number needed to treat to prevent a lethal reaction in high-risk patients to be 50,000 [30].

There are no studies evaluating the efficacy of premedication prior to oral contrast medium administration or gadolinium-based contrast medium administration in high-risk patients. Premedication strategies in these patients are based on extrapolated data from patients receiving intravascular iodinated media.

Risks of Premedication: The direct risks of premedication are small [31] and include transient leukocytosis, transient (24-48h) and usually asymptomatic hyperglycemia (non-diabetics: +20-80 mg/dL, diabetics: +100- 150 mg/dL) [32, 33], and a questionable infection risk, among other things. Diphenhydramine may cause drowsiness and should not be taken shortly before operating a vehicle. Some patients have experienced allergies to the individual medications used in premedication.

The largest risk of premedication is indirect and related to the delay in diagnosis imparted by the multi- hour duration of premedication [30]. In one retrospective cohort study of 2829 subjects, 13-hour oral premedication of high-risk inpatients was associated with increased hospital length of stay (median: +25h), increased time to CT (median: +25h), increased hospital-acquired infection risk, and increased costs compared to non-premedicated controls [30]. The indirect harms of premedication likely overshadow the benefits of premedication in some vulnerable populations.

Breakthrough Contrast Reactions: Premedication does not prevent all contrast reactions [29,34,35]. Allergic- like contrast reactions that occur despite premedication are called “breakthrough reactions” [34]. Physiologic reactions are not mitigated by premedication and are not considered “breakthrough reactions,” even if they occur following premedication.

Patients premedicated for a prior contrast reaction have a breakthrough reaction rate (2.1%) that is 3-4 times the ordinary reaction rate in the general population, while patients premedicated for other indications have a breakthrough reaction rate close to 0% [29]. In most cases (~81%), breakthrough reaction severity is similar to index reaction severity [34, 35]. Patients with a mild index reaction have a very low risk (<1%) of developing a severe breakthrough reaction [29].

The majority (~88%) of contrast injections in premedicated patients with a prior breakthrough reaction will not result in a repeat breakthrough reaction [34, 35]. Repeat breakthrough reactions, if they occur, usually are of similar severity to prior breakthrough reactions. Therefore, patients who have had a prior moderate or severe breakthrough reaction are at the highest risk for developing a future moderate or severe breakthrough reaction [34,35].

Premedication Strategies: Oral premedication is preferable to IV premedication in most settings due to lower cost, more convenience, and greater evidentiary support in the literature [22, 27]. The randomized trials of premedication in average-risk patients were conducted with oral methylprednisolone [22, 27]. Uncontrolled studies in high-risk patients were conducted with oral prednisone [36, 37].

Supplemental administration of a non-selective antihistamine (e.g., diphenhydramine) orally or intravenously 1 hour prior to contrast medium administration may reduce the frequency of urticaria, angioedema, and respiratory symptoms. Use of selective anti-histamines (i.e., selective H2 blockers) has not been well studied [36].

The minimum duration of premedication necessary for efficacy is unknown. Lasser et al [27] showed that one dose of 32 mg oral methylprednisolone 2 hours prior to IV high-osmolality iodinated contrast medium administration in average-risk patients was not effective, while two doses administered at 2- and 12-hours before contrast medium administration were effective [27].

A dose-response study of single-dose IV methylprednisolone (1 mg/kg) [38] in 11 volunteers showed a reduction in circulating basophils and eosinophils by the end of the first post-injection hour, reaching statistical significance compared with controls by the end of the second hour and a concomitant reduction in histamine in sedimented leukocytes by 4 hours. Most of these effects reached their peak at 8 hours.

There is no evidence to support a premedication duration of 2 hours or less (oral or IV; corticosteroid- or antihistamine-based).

An IV corticosteroid regimen with a minimum duration of 4-5 hours may be efficacious [11, 27, 31, 38].

Indications for Premedication

Given that premedication does not prevent all reactions, has not been confirmed to reduce the incidence of moderate or severe reactions or reaction-related deaths, has limited supporting efficacy in high-risk patients, and is accompanied by direct and indirect harms, the utility of premedication in high- risk patients is uncertain. Given the tradeoffs between what is known and not known with respect to the benefits and harms of premedication, premedication may be considered in the following settings and scenarios:

12- or 13-hour oral premedication maybe considered in the following settings:

1. Outpatient with a prior allergic-like or unknown-type contrast reaction to the same class of contrast medium (e.g., iodinated – iodinated).

2. Emergency department patient or inpatient with a prior allergic-like or unknown-type contrast reaction to the same class of contrast medium (e.g., iodinated – iodinated) in whom the use of premedication is not anticipated to adversely delay care decisions or treatment.

Accelerated IV premedication may be considered in the following settings:

1. Outpatient with a prior allergic-like or unknown-type contrast reaction to the same class of contrast medium (e.g., iodinated – iodinated) who has arrived for a contrast-enhanced examination but has not been premedicated and whose examination cannot be easily rescheduled.

2. Emergency department patient or inpatient with a prior allergic-like or unknown-type contrast reaction to the same class of contrast medium (e.g., iodinated – iodinated) in whom the use of 12- or 13-hour premedication is anticipated to adversely delay care decisions or treatment.

In rare clinical situations, the urgency of a contrast-enhanced examination may outweigh the benefits of prophylaxis, regardless of duration, necessitating that contrast medium be administered to a high-risk patient in the absence of premedication. This determination is best made jointly by the radiology team, the referring service, and potentially the patient (if feasible). In such cases, a team of individuals skilled in resuscitation should be available during the injection to monitor for and appropriately manage any developing reaction.

Regardless of patient status, history of a prior severe contrast reaction is considered a relative contraindication to receiving the same class of contrast medium in the future. If the same class of contrast medium is necessary and there are no alternatives, premedication should be considered if feasible.

Routine premedication or avoidance of contrast medium for other indications, such as allergic reactions to other substances (including shellfish or contrast media from another class [e.g., gadolinium-based – iodinated]), asthma, seasonal allergies, or multiple drug and food allergies is not recommended.

Specific Recommended Premedication Regimens

Elective Premedication (12- or 13-hour oral premedication)

1. Prednisone-based: 50 mg prednisone by mouth at 13 hours, 7 hours, and 1 hour before contrast medium administration, plus 50 mg diphenhydramine intravenously, intramuscularly, or by mouth 1 hour before contrast medium administration [22].

Or

2. Methylprednisolone-based: 32 mg methylprednisolone by mouth 12 hours and 2 hours before contrast medium administration. 50 mg diphenhydramine may be added as in option 1 [39].

Although never formally compared, both regimens are considered similarly effective. The presence of diphenhydramine in regimen 1 and not in regimen 2 is historical and not evidence-based. Therefore, diphenhydramine may be considered optional.

If a patient is unable to take oral medication, option 1 may be used substituting 200 mg hydrocortisone IV for each dose of oral prednisone [40]. If a patient is allergic to diphenhydramine in a situation where diphenhydramine would otherwise be considered, an alternate anti-histamine without cross-reactivity may be considered, or the anti-histamine portion of the regimen may be dropped.

Accelerated IV Premedication (in decreasing order of desirability)

1. Methylprednisolone sodium succinate (e.g., Solu-Medrol®) 40 mg IV or hydrocortisone sodium succinate (e.g., Solu-Cortef®) 200 mg IV immediately, and then every 4 hours until contrast medium administration, plus diphenhydramine 50 mg IV 1 hour before contrast medium administration. This regimen usually is 4-5 hours in duration.

2. Dexamethasone sodium sulfate (e.g., Decadron®) 7.5 mg IV immediately, and then every 4 hours until contrast medium administration, plus diphenhydramine 50 mg IV 1 hour before contrast medium administration. This regimen may be useful in patients with an allergy to methylprednisolone and is also usually 4-5 hours in duration.

3. Methylprednisolone sodium succinate (e.g., Solu-Medrol®) 40 mg IV or hydrocortisone sodium succinate (e.g., Solu-Cortef®) 200 mg IV, plus diphenhydramine 50 mg IV, each 1 hour before contrast medium administration. This regimen, and all other regimens with a duration less than 4-5 hours, has no evidence of efficacy. It may be considered in emergent situations when there are no alternatives.

Note: Premedication regimens less than 4-5 hours in duration (oral or IV) have not been shown to be effective. The accelerated 4-5-hour regimen listed as Accelerated IV option 1 is supported by a case series and by a retrospective cohort study with 828 subjects [40].

Missing One or More Doses of Premedication

Sometimes, patients undergoing premedication present for a contrast-enhanced scan without completing their premedication regimen. In such cases, there is no evidence base to guide decision-making, so management should be individualized. Generally speaking, if premedication is being used, a guiding principle is to have a minimum of 4-5 hours of corticosteroid therapy prior to contrast medium exposure, with repeat doses every 4-8 hours. Diphenhydramine administration is optional.

Premedication in Patients Undergoing Chronic Corticosteroid Therapy

In patients who have had a prior allergic-like reaction to contrast medium and who are also on chronic corticosteroid therapy, premedication dosing may be modified. In this circumstance, there is no evidence base to guide decision-making, so management should be individualized. Generally speaking, if corticosteroid premedication is being used, a guiding principle is to reduce the dose of the chosen premedication dose regimen by an amount equivalent to the patient's chronic therapeutic corticosteroid dose. If the patient is on simple replacement (not therapeutic) corticosteroids, the premedication dosing regimen may not need to be adjusted.

Changing Contrast Media Within the Same Class

In patients with a prior allergic-like or unknown-type contrast reaction to a known contrast medium, changing contrast media within the same class (e.g., one iodinated medium for another) may help reduce the likelihood of a subsequent contrast reaction [41,42]. Some studies have shown that the effect size of switching contrast media actually may be greater than that of premedication alone, but combining premedication with a change in agent seems to have the greatest effect [41,42]. Unfortunately, many patients do not know which specific agent they have reacted to in the past;

they simply remember they had a reaction. In the future, through improved electronic medical records, routine linking of reactions to specific contrast media is likely to add value. In the current state, investigating which agent was responsible for one or more prior reactions often is not possible.

Premedication Is Not a Panacea

No premedication strategy is a substitute for pre-administration preparedness. Contrast reactions occur despite premedication [34], and radiology teams must be prepared to treat breakthrough reactions when they occur. Patients should receive information concerning their risk of a reaction according to local policy and practice.

References

1. Wang CL, Cohan RH, Ellis JH, Caoili EM, Wang G, Francis IR. Frequency, outcome, and appropriateness of treatment of nonionic iodinated contrast media reactions. AJR Am J Roentgenol 2008; 191 (2):409-15, PMID: 18647910.
2. Herranz L, Bordas J, Towns-Andrews E, Mendez E, Usobiaga P, Carrascosa JL. Conformational changes in bacteriophage phi 29 connector prevents DNA-binding activity. J Mol Biol 1990; 213 (2):263-73, PMID: 2342107.
3. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. Radiology 1990; 175 (3):621-8, PMID: 2343107.
4. Jung JW, Kang HR, Kim MH, Lee W, Min KU, Han MH, Cho SH. Immediate hypersensitivity reaction to gadolinium-based MR contrast media. Radiology 2012; 264 (2):414-22, PMID: 22550309.
5. Beaty AD, Lieberman PL, Slavin RG. Seafood allergy and radiocontrast media: are physicians propagating a myth? Am J Med 2008; 121 (2):158 e1-4, PMID: 18261505.
6. Boehm I. Seafood allergy and radiocontrast media: are physicians propagating a myth? Am J Med 2008; 121 (8):e19, PMID: 18691465.
7. Shehadi WH. Adverse reactions to intravascularly administered contrast media. A comprehensive study based on a prospective survey. Am J Roentgenol Radium Ther Nucl Med 1975; 124 (1):145-52, PMID: 1170768.
8. Lalli AF. Urographic contrast media reactions and anxiety. Radiology 1974; 112 (2):267-71, PMID: 4600651.
9. Callahan MJ, Poznauskis L, Zurakowski D, Taylor GA. Nonionic iodinated intravenous contrast material-related reactions: incidence in large urban children's hospital--retrospective analysis of data in 12,494 patients. Radiology 2009; 250 (3):674- 81, PMID: 19244041.
10. Lang DM, Alpern MB, Visintainer PF, Smith ST. Elevated risk of anaphylactoid reaction from radiographic contrast media is associated with both beta-blocker exposure and cardiovascular disorders. Arch Intern Med 1993; 153 (17):2033-40, PMID: 8102844.
11. Morcos SK. Review article: Acute serious and fatal reactions to contrast media: our current understanding. Br J Radiol 2005; 78 (932):686-93, PMID: 16046418.
12. Mukherjee JJ, Peppercorn PD, Reznek RH, Patel V, Kaltsas G, Besser M, Grossman AB. Pheochromocytoma: effect of nonionic contrast medium in CT on circulating catecholamine levels. Radiology 1997; 202 (1):227-31, PMID: 8988215.
13. Mehrizi M, Pascuzzi RM. Complications of radiologic contrast in patients with myasthenia gravis. Muscle Nerve 2014; 50 (3):443-4, PMID: 24677227.
14. Somashekar DK, Davenport MS, Cohan RH, Dillman JR, Ellis JH. Effect of intravenous low-osmolality iodinated contrast media on patients with myasthenia gravis. Radiology 2013; 267 (3):727-34, PMID: 23360741.
15. van der Molen AJ, Thomsen HS, Morcos SK. Effect of iodinated contrast media on thyroid function in adults. Eur Radiol 2004; 14 (5):902-7, PMID: 149973340.
16. Medicine SoN. Therapy of Thyroid Disease with Iodine-131 v2.0.pdf. http://interactive.snm.org/docs/Therapy%20of%20Thyroid%20Disease%20with%20Iodine-131%20v2.0.pdf, 2017.
17. Silberstein EB, Alavi A, Balon HR, Clarke SE, Divgi C, Gelfand MJ, Goldsmith SJ, Jadvar H, Marcus CS, Martin WH, Parker JA, Royal HD, Sarkar SD, Stabin M, Waxman AD. The SNMMI practice guideline for therapy of thyroid disease with 131I 3.0. J Nucl Med 2012; 53 (10):1633-51, PMID: 22787108.
18. Palena LM, Sacco ZD, Brigato C, Sultato E, Barra D, Candeo A, Manzi M. Discomfort assessment in peripheral angiography: randomized clinical trial of Iodixanol 270 versus Ioversol 320 in diabetics with critical limb ischemia. Catheter Cardiovasc Interv 2014; 84 (6):1019-25, PMID: 24478190.
19. Laroche D, Aimone-Gastin I, Dubois F, Huet H, Gerard P, Vergnaud MC, Mouton-Faivre C, Gueant JL, Laxenaire MC, Bricard H. Mechanisms of severe, immediate reactions to iodinated contrast material. Radiology 1998; 209 (1):183-90, PMID: 9769830.