Mount Sinai Health System Radiology Contrast Premedication Committee
November 2, 2015

Purpose:

The MSHS Radiology Contrast Premedication Committee was convened to assess the available literature regarding contrast reactions, and to develop a clear understanding and workflow regarding pre-medication in patients prior to intravascular contrast administration.

Brief Overview:

The current *ACR Manual on Contrast Media* (v10.1, 2015) lacks absolute clarity regarding whom to pre-medicate and why. This confusion is manifold. 1) Terminology regarding reactions is vague and statements are sometimes confusing and ambiguous. 2) There is often no distinction between "contrast reactions" and their more problematic subset of "severe contrast reactions," or between "prior allergy-like reaction to contrast media" and "any allergic diasthesis." 3) No frank data has been supplied within the guidelines themselves, and many references are dated, refer to older varieties of contrast or refer among few authors in a circular pattern such that primary data is more sparse than it seems.

This committee was convened to delve deeper into the references provided in the ACR document itself, as well as other available relevant data and literature. We have also reviewed policies from other hospitals such as Yale and MGH.

These guidelines are written with the clear understanding that our goal is to minimize the incidence of ***severe*** adverse reactions to contrast agents in a regimen that is practicable and not overly onerous. Although it is desirable to avoid all contrast reactions (including mild and moderate), premedicating patients to avoid these less significant problems is neither practical nor reflects the standard of care in other large academic medical centers. It is worth mentioning as a substrate that since we no longer use high osmolar contrast agents, our reactions are considerably less frequent than they had been in literature historically.

Key conclusions:

1) There are no data showing an increased rate of severe contrast reactions in patients receiving low osmolar contrast who have had previous adverse food or drug reactions.

2) Patients who have had previous moderate-to-severe contrast reactions benefit from a combination of pre-medication and switch to a different contrast agent.

3) Breakthrough reactions (repeat reactions despite premedication) cannot be avoided and staff must be available for resuscitation and/or intubation when studies are performed on these patients.

Future goals:

With unification of premedication practices under one policy across all sites of the Department of Radiology, collection of data may prove useful to confirm that the proposed level of vigilance and pre-medication is most suitable for the patient population and reflects reaction rates at among peer institutions.

Membership:

Scott Nowakowski MD, Interventional Radiologist and Committee Chairman
Emma Acasio RN, Radiology Associates Staff nurse
Jamie Altabet MD, MSBI Radiology Resident (excused 02 Nov 2015)
Jeanne Ambroise RN, Nurse Manager at Radiology Associates (excused 02 Nov 2015)
Tina Berler RN, MSSLR Nurse Manager
Bradley Delman MD, Vice Chair for Quality, PI and Clinical Research
Donna Dibenedetto, Nurse Manager at MSBI
Corey Eber MD MHA, Vice Chair for Operations
James Fox, Operations Manager MSR
Hyunjoo Han RN, Clinical Nurse Mount Sinai Hospital
Emmanuel Hidalgo RT, MSR CT supervisor
Will Javier, CT Supervisor for MSBI (excused 02 Nov 2015)
Alexander Kagen MD, MSSLR Site Director
Nolan Kagetsu MD, MSSLR Quality
Nancy Lamberson RN MS, Associate Director of Nursing (MSH)
Valerie Maccarrone MD, MSBISLR attending radiologist
Alexandra Roudenko MD, MSSLR Radiology Resident (excused 02 Nov 2015)
Vikram Sundaram MD, Radiology Resident (MSH)
Barbara Zeifer MD, Site Director of MSBI
Stephen Zink MD, MSBI Quality (excused 02 Nov 2015)

MOUNT SINAI DEPARTMENT OF RADIOLOGY

Guidelines for Patient Selection & Premedication Strategies for Intravascular Contrast

(Endorsed by MSHS Contrast Premedication Committee, November 2, 2015)

1. BACKGROUND: RISK FACTORS FOR IODINATED CONTRAST REACTIONS

ALLERGY. Incidence with LONIC is on the order of 0.01 - 0.02% (?ref). With regard to specific risk factors, a history of a prior allergic-like reaction to contrast media is associated with an up to five-fold (5x) increased likelihood of the patient experiencing a subsequent reaction. Note that while any allergic diathesis may modestly increase risk for reaction to contrast, the relationship between non-contrast allergies and contrast allergies remains difficult to define. Furthermore, many individuals have at least one minor allergy, such as seasonal rhinitis, and the overwhelming majority of these patients do not experience reaction to non-ionic contrast routinely employed. Although The ACR states that "True concern should be focused on patients with significant allergies, such as a prior major anaphylactic response to one or more allergens," they also state "Although mild reactions to contrast media are relatively common, they are almost invariably self-limited and of no consequence" and "Severe, life-threatening reactions, although rare, can occur in the absence of any specific risk factors with any type of media." Evaluation of the available source data and ACR references was therefore performed. Examples include:

- Katayama et. al. (*Radiology*, 1990): "**No positive effect (on patients with history of allergy) due to premedication was observed in the nonionic contrast media group. We conclude that nonionic contrast media render premedication unnecessary in patients at risk because of a history of allergy**."

- Lasser et. al. (*AJR*, 1994): "**Controlling for the history and severity of previous reaction had essentially no effect on the finding of a decreased rate or reaction among patients pre-treated with corticosteroids** … In summary, then, methylprednisolone was shown to decrease the occurrence of overall reactions and grade I reactions (p = .004), but **not grade II reactions (p = .63) or grade III reactions (p = .11**)."

- Abe et. al. (*Eur Radiol*, 2015): "Compared with nonpremedicated patients, the frequency of total adverse reactions decreased significantly, however, **the frequency of Grade 1 to 3 reactions did not decrease significantly**. The premedication effect seemed limited in our study." This study advocated *changing contrast medium* as a possible protective effect.

ASTHMA. A history of asthma may portend an increased likelihood of a contrast reaction. Patients with current asthmatic attacks should have their contrast study re-scheduled whenever possible.

CONTRAST REACTIONS. The severity of contrast reaction can vary. The ACR classification scheme of allergic-like contrast reactions is as follows:

MILD	MODERATE	SEVERE
Limited urticaria /pruritis Limited cutaneous edema Limited "itchy"/"scratchy" throat Nasal congestion	Diffuse urticaria /pruritis Diffuse erythema with stable vital signs Facial edema without dyspnea Throat tightness or hoarseness without dyspnea Wheezing / bronchospasm, mild or no hypoxia	Diffuse edema, or facial edema with dyspnea Diffuse erythema with hypotension Laryngeal edema with stridor and/or hypoxia Wheezing / bronchospasm, with significant hypoxia Anaphylactic shock (hypotension + tachycardia)

2. PREMEDICATION

The primary indication for premedication is pretreatment of "at-risk" patients who require contrast media. In this context, "at risk" reflects a higher risk for an acute allergic-like reaction, and ***it is most important to target premedication to i) those who, in the past, have had moderate to severe allergic-like reactions to iodinated contrast***. Assessment of reaction severity is somewhat subjective, and it is difficult to succinctly describe all possible degrees of reaction severity. Please refer to Appendix 1 of this document for decision flowcharts to determine whether premedication is necessary.

Oral administration of steroids is preferable to IV administration, and prednisone and methylprednisolone are equally effective. It is preferred that steroids be given beginning at least 6 hours prior to the injection of contrast media regardless of the route of steroid administration whenever possible. It is unclear if administration a steroid premedication window of fewer than four hours actually reduces adverse reactions. Supplemental administration of an H-1 antihistamine (e.g., diphenhydramine), orally or intravenously, may reduce the frequency of urticaria, angioedema, and respiratory symptoms.

Patients requiring premedication should be scheduled and performed at sites with primary response teams available to treat reactions promptly.

Whenever possible, the contrast agent should be modified from prior allergy-associated contrast, if that prior agent is known.

A. PREMEDICATION IN NON-EMERGENT CASES. IN THESE CASES, CONTRAST AGENT SHOULD BE CHANGED FROM PREVIOUS AGENT THAT CAUSED REACTION. Two frequently used regimens are:

1. Prednisone
50 mg PO
13h, 7h & 1h before contrast injection

Plus

2. Diphenhydramine (Benadryl®)
50 mg IV, IM or PO
1 hour before contrast

1. Methylprednisolone (Medrol®)
32 mg PO
12h & 2h before contrast injection

And also (if possible)

2. Diphenhydramine (Benadryl®)
50 mg IV, IM or PO
1 hour before contrast

B. PREMEDICATION IN EMERGENT CASES. IN THESE CASES, CONTRAST AGENT SHOULD BE CHANGED FROM PREVIOUS AGENT THAT CAUSED REACTION. The first regimen is preferred, but two other options exist as necessary:

PREFERRED:

1. Steroid at least 4 hours before contrast, and repeated every 4 hours as necessary:
Methylprednisolone sodium succinate (Solu-Medrol®)
40 mg IV

or

Hydrocortisone sodium succinate (Solu-Cortef®)
200 mg IV

Plus

2. Diphenhydramine (Benadryl®)
50 mg IV
1 hour before contrast

LESS DESIREABLE (use for allergy to methylprednisolone or aspirin or NSAIDs):

1. Steroid, every 4 hours:
Dexamethasone sodium sulfate (Decadron®)
7.5 mg IV

or

Betamethasone
6.0 mg IV

Plus

2. ***Diphenhydramine (Benadryl®)***
50 mg IV
1 hour before contrast

LEAST DESIREABLE:

Omit steroids (steroids are relatively ineffective in the first 4-6 hours)

Instead give

Diphenhydramine (Benadryl®)
50 mg IV
1 hour before contrast

3. COMMENTS/RECOMMENDATIONS FOR IODINATED CONTRAST

A. Although non-asthmatics with severe allergic-like reactions to any food or medication may be at modest increased risk for allergic-type contrast reaction of any type, the inconvenience, cost and delay for premedication in such patients is likely not justified.

B. Most patients with a history of **allergic-like reactions to agents other than iodinated contrast** and patients with a history of only **physiologic reactions** to any substance (including nausea/vomiting, flushing, headaches/dizziness, hypertension and vasovagal reactions) **do not typically require premedication**.

C. When clinical circumstances warrant, the premedication regimen can be shortened (see "Emergency Premedication" above) to 4 or 8 hours or disregarded entirely depending on the urgent need of the examination balanced against the perceived risk of iodinated contrast as determined and documented by the referring physician.

D. For patients with moderate or severe reactions to iodinated contrast, consideration should be given to non-contrast imaging or use of an alternate modality such as MR or sonography whenever possible.

E. Because interventional procedures are performed directly by physicians, who can monitor patients during and after contrast injections, the eligibility for premedication may be modified by an Interventional Radiologist performing such procedures as patient circumstances warrant.

4. CONSIDERATIONS FOR GADOLINIUM-BASED CONTRAST MEDIA (GBCM)

Severe and even life threatening allergic-like reactions to GBCM are uncommon and vary in frequency from .01 - .001%. The frequency of acute adverse reactions to GBCM is about eight times higher in patients with a previous reaction to GBCM. A prior allergic-like reaction to GBCM is often an indication for corticosteroid prophylaxis prior to subsequent exposures, as described in Section 2 above.

Patients with asthma and various other allergies may have a mild increased risk for an allergic-like reaction to GBCM compared to the general population, but as with iodinated contrast, no additional premedication would be necessary based on the presence of asthma alone given the extremely low overall reaction rate for GBCM.

There is no cross-reactivity between GBCM and iodinated contrast media, and therefore allergic-type sensitivity to one is not, by itself, a reason to premedicate for the other.

APPENDIX 1.

Department of Radiology, Mount Sinai Health System
Contrast Premedication Decision Trees **(Nov 02, 2015)**

IODINATED (CT & IR) CONTRAST

"If you have had IODINATED contrast before, has there been a MODERATE OR SEVERE allergic-type reaction (including ANAPHYLAXIS)?"

"NO" or "I DON'T KNOW" → PROCEED AS ORDERED

"YES" OR "I THINK SO" → 1) PREMEDICATION REGIMEN 2) CHANGE CONTRAST AGENTS

Note: For clarity, the following types of patients do **NOT** ordinarily require premedication:

- *Patients with "SHELLFISH ALLERGY"*
- *Patients with MILD IODINATED contrast reactions*
- *Patients with allergies to other FOOD/MEDICATIONS (including asthma induced by allergens other than contrast)*
- *Patients with SEASONAL ALLERGIES*

GADOLINIUM (MRI) CONTRAST

"If you have had GADOLINIUM contrast before, has there been a MODERATE OR SEVERE allergic-type reaction (including ANAPHYLAXIS)?"

"NO" or "I DON'T KNOW" → PROCEED AS ORDERED

"YES" OR "I THINK SO" → 1) PREMEDICATION REGIMEN 2) CHANGE CONTRAST AGENTS

Note: For clarity, the following types of patients do **NOT** ordinarily require premedication:

- *Patients with MILD GADOLINIUM contrast reactions*
- *Patients with allergies to other FOOD/MEDICATIONS (including asthma induced by allergens other than contrast)*
- *Patients with SEASONAL ALLERGIES*

Grading of Allergic-type Contrast Reactions

Mild	Moderate	Severe
Limited urticaria /pruritis	Diffuse urticaria /pruritis	Diffuse edema, or facial edema with dyspnea
Limited cutaneous edema	Diffuse erythema with stable vital signs	Diffuse erythema with hypotension
Limited "itchy"/"scratchy" throat	Facial edema without dyspnea	Laryngeal edema with stridor and/or hypoxia
Nasal congestion	Throat tightness or hoarseness without dyspnea	Wheezing / bronchospasm, with significant hypoxia
	Wheezing / bronchospasm, mild or no hypoxia	Anaphylactic shock (hypotension + tachycardia)

APPENDIX 2. COMPREHENSIVE LITERATURE REVIEW

Background:

It is known that patients may experience an adverse reaction to intravenously administered contrast media. These reactions are considered to be either allergic-like or physiologic, depending on the response evoked in the patient. Of note, allergic-like reactions can be treated as if they were allergic reactions, while physiologic reactions are treated with supportive measures. Both types of reactions are graded as mild, moderate or severe, and both types (though typically considered in allergic-like) may be immediate (within 1 hour) or delayed (between 1 hour and 7 days). The mechanism by which these adverse reactions occur remains unclear, as no models have clearly demonstrated the pathway or pathways by which intravenous contrast media causes adverse reactions [1].

Research from the 1980s and 1990s (discussed below, see Lasser, Greenberger, and Katayama) has shown that premedication protocols have the effect of reducing adverse reactions to intravenously administered high-osmolarity ionic contrast media (HOIC). Current research regarding adverse reactions to intravenously administered low-osmolarity nonionic contrast media (LONIC) and the effect of premedication protocols, however, is mixed. Furthermore, no studies to date demonstrate that premedication protocols have an effect on severe adverse reactions to LONIC. In addition, despite the use of premedication, breakthrough reactions may occur, often of the same severity index, in an overall unpredictable fashion.

These facts have made it difficult to make a clear recommendation on the most efficacious use of premedication protocol in patients who may be at risk for adverse reactions. Therefore, this review seeks to clarify the current data supporting the use of premedication protocol and its optimal use in the hospital setting regarding currently used intravenous contrast media.

Methods:

A focused literature review was performed, searching for relevant articles on PubMed, primarily within the last 5 years (2010-2015), with relevance to adverse reactions to intravenous contrast media and the question of premedication efficacy in reducing the rate of mild, moderate, and severe reactions. Additionally, a review of the major points and the data supporting the current ACR guidelines was performed.

Data:

Estimated rates of adverse reactions to contrast media

Research by Katayama (1990) demonstrated that 3.13% of patients (5,276 of 168,363) had adverse reactions to LONIC. Of these, 0.04% (70 of 168,363) was severe. 1 death occurred in the group of patients receiving LONIC during this study, and the death demonstrated no causal relation to intravenous LONIC administration [12].

Research by Mortelé (2005) demonstrated that 0.7% of patients (211 of 29,508),over a 2-year period, experienced adverse reaction to contrast media (89% mild, 9% moderate, and 2% severe) [20].

Research by Davenport (2009) demonstrated that 0.7% of injections (1044 of 140,753) resulted in adverse reactions (928 mild, 99 moderate, 17 severe). Of the 1044 adverse reactions, 198 were breakthrough reactions after premedication (153 mild, 35 moderate, 3 severe) [6].

Risk factors for repeat adverse reactions

Certain patients are thought to be more likely to experience an adverse reaction. The most commonly cited risk factor for having a potential adverse reaction to intravenously administered contrast media is a prior reaction. This risk factor is generally strong across multiple studies [4, 12, 19, 6, 23, 24]. General atopy, whether manifest as drug allergies, food allergies, or asthma, is also commonly suggested as putting a patient at an increased risk for having an adverse reaction, specifically allergic-like. The data supporting these latter risk factors is not as clear, and it is not reproduced with as much confidence as the risk factor of prior adverse reaction [23]. Still, it has been observed that patients who have had a prior adverse reaction can receive intravenous contrast media and not have a current adverse reaction (Shehadi 1975) [21].

Reasons for calling adverse reactions "allergic/allergic-like."

Research by Lasser (1987, AJR) attempted to explain the observation that patients with predisposition to allergies were more likely to have allergic-like reactions to intravenous contrast media. He suggests that atopic patients are "primed" to undergo an allergic-like reaction. He suggests that HOIC can cause ACE-inhibition, leading to prolonged activity of bradykinin as part of an allergic cascade. He does not produce evidence for the actual mechanism by which HOIC results in an allergic-like response, but suggests a model involving complement activation, bradykinin activation, and induction of mast cells. Based on his papers, he reaches the conclusion that, since corticosteroids reduces the "primed" state in allergic patients, it may have benefit in reducing contrast reactions [15].

Research by Laroche (1998) compared histamine levels in 20 patients who experienced immediate adverse reaction to intravenous contrast media (of varying osmolarity) to 20 control patients. 90% of adverse reactions occurred when giving ionic contrast media. There was a statistically significant increase in the level of histamine in patients who experienced immediate adverse reaction when compared to control patients who did not have an adverse reaction. The same observation was seen regarding tryptase levels (as a marker of mast cells). Based on these findings, this paper suggests using premedication in patients at risk for mild adverse reactions, citing Lasser's 1987 NEJM article (described below). This paper notes that premedication (which in their study was not consistently implemented) had no effect in preventing severe adverse reactions in their study [14].

Research by Greenberger (1988) discussed the confusion regarding allergic-like reactions caused by intravenous contrast media, including the fact that reactions may occur during a patient's first introduction to contrast media, that IgE seems to be implicated (based on the observation of urticaria) but cannot be directly linked to contrast media adverse reactions, and that repeat reactions may be inconsistent in either appearance or in degree of severity [9].

High-osmolarity ionic contrast media adverse reactions are reduced by premedication

Research by Greenberger (1988) using several variations of his premedication protocol demonstrates that of 945 injections of HOIC to patients with a previous immediate adverse reaction, 73 "immediate generalized" (allergy-like) reactions occurred (of which 64 were mild and 3 were severe), and that of 167 serious/severe reactions (both allergic-like and physiologic), only 12 breakthrough reactions occurred. Based on this data, Greenberger concluded that premedication resulted in the decrease in repeat reactions in these high-risk patients. Of note, Greenberger does not specifically list all types of adverse reactions that are categorized, making it difficult to compare his data to the current standard classification of allergic-like or physiologic reactions put forth by the ACR and other researchers. For instance, he considers syncope and bradycardia as possible severe reactions, despite the fact that these are now considered physiologic and thus would not be affected by a premedication protocol [9].

Research by Lasser (1987, NEJM) demonstrated that adverse reactions to HOIC were reduced using a premedication protocol that his group devised. Of note, his paper also demonstrates that HOIC with premedication has a similar percentage of adverse reactions requiring therapy when compared to LONIC administered *without* premedication, demonstrating the better safety profile of LONIC [16].

Research by Katayama (1990) demonstrated that premedication reduced the number of severe adverse reactions to HOIC in patients with a history of allergy. This same effect was not observed in patients without a history of allergy. The same article also demonstrated that there was no clear effect of premedication on either "all adverse reactions," or on "severe adverse reactions" in patients receiving LONIC [12].

Research by Greenberger (1991), using his 13-hour protocol, had shown that premedicating patients who have had a prior adverse reaction to high-osmolarity ionic contrast media results in a reduced incidence of a second adverse reaction. This paper does not compare premedication to a control setting [10].

A review article by Bush (1991) cited Greenberger (1985) and Lasser (1987, NEJM) as studies that demonstrated the positive benefit of premedication in decreasing the rate of repeat adverse reactions. Both of these papers primarily studied effects of premedication on HOIC. The review article by Bush is cited by the ACR as additional evidence of the benefit of premedication [1, 5].

Low-osmolarity nonionic contrast media mild adverse reactions may be reduced by premedication

Research by Lasser (1994) examined adverse reactions after intravenous administration of LONIC in 10 patients (out of 580) under premedication protocol versus 28 patients (out of 575) using a control protocol. There was a statistically significant decrease in overall adverse reactions (mild, moderate, and severe) with premedication versus control and in mild adverse reactions with premedication versus control. Lasser admits that the number of patients in his

study is small, but draws a conclusion that premedication has a statistically significant benefit. He cites his own paper from 1987 regarding HOIC as a reason for drawing his conclusion. He cites his own papers on HOIC and premedication to suggest the likely mechanisms of protection afforded by premedication [17].

Research by Jingu (2014) performed a retrospective study analyzing patients who received a Lasser 12 hour premedication protocol, either because of a prior reaction or because of a history of asthma. Of 117 patients with a prior adverse reaction, 7 mild and 1 moderate adverse breakthrough reactions occurred after premedication. They argued that a prospective study in which patients with a prior adverse reaction are given a control protocol may be unethical, making it difficult to truly determine whether premedication has a tangible benefit. Nevertheless, they conclude that premedication seems to be of some benefit in reducing breakthrough reactions [11].

Research by Katayama (1990) demonstrated that no positive effect of premedication was seen in LONIC compared to patients who did not receive premedication [12].

Research by Kolbe (2014) used multivariate analysis regarding 50 patients whose first adverse reaction to LONIC was mild urticaria. The study paradoxically demonstrated an *increased* risk of breakthrough reaction in those patients receiving premedication compared to those who did not, suggesting that premedication had no benefit in preventing adverse outcomes. The paper did additionally note that LONIC has a better safety profile than HOIC [13].

Research by Abe (2015) in a non-blinded, non-randomized prospective study where 771 patients with previous adverse reaction were given either the same type of LONIC with or without premedication, or a different type of LONIC with or without premedication. In the group where the type of LONIC was the same but premedication was either used or not, the total number of adverse reactions did not show a statistically significant decrease when considering all severity grades of adverse reactions [2].

Severe reactions to low-osmolarity nonionic contrast are rare and difficult to accurately study

The ACR cites Greenberger (1991) regarding the fact that premedication reduces the number of adverse reactions to contrast. However, the article in question by Greenberger notes that severe adverse reactions do not seem to be affected by premedication protocol, in agreement with Katayama (1990). The article by Greenberger cites Lasser (1987, NEJM) regarding premedication as effective for mild adverse reactions, yet that article by Lasser in NEJM compared HOIC with premedication to LONIC without premedication and found a similar safety profile. Therefore, the ACR is only able to demonstrate that HOIC is affected by premedication, while no effect on LONIC is clearly demonstrated [1, 10, 12, 16].

Research by Freed (2001) admits that breakthrough reactions of similar severity index do occur despite premedication. The paper still recommends premedication in patients who have had prior severe adverse reaction to contrast, though it also recommends that a code team or rapid response team be present or readily available in the event of a breakthrough reaction [7].

Research by Tramèr (2006) puts the potential number needed to treat to prevent a severe adverse reaction at 100-150. This number is based on the trial by Lasser in 1987 [22, 16].

Research by Mervak (2015) estimates the number needed to treat to prevent a severe adverse reaction at 569, or 289 days of pretreatment using a 12-hour premedication protocol. This calculation is based on data from Katayama (1990) and Wang (2008) [18, 12].

Research by Morcos (2001, 2005) suggests that the mechanism by which premedication is protective is not understood. The protective nature of premedication that Morcos suggests is based on earlier recommendations by Lasser and Greenberger. Morcos admits that patients who are premedicated can still experience severe and/or life-threatening adverse reactions [19].

Discussion and Recommendations:

Despite a lack of understanding of the mechanisms of adverse reaction to contrast media, the current *ACR Manual on Contrast Media*(v10.1, 2015) continues to rely on studies performed on HOIC that do demonstrate some appreciable positive effect of premedication and lower rates of adverse reactions. The assumption seems to be that adverse reactions to HOIC must have a similar mechanism to LONIC. This assumption may be misleading, as LONIC clearly has much better safety profile than HOIC. The best example of this fact comes from Lasser (1987, NEJM), where the percent of patients requiring therapy after either injection of HOIC with premedication, or injection of LONIC without premedication, were not statistically different [16]. This same observation was noted by Greenberger in 1991 [10]. Additionally, one of the more powerful studies in terms of patients enrolled (nearly 170,000), performed by Katayama (1990), did not demonstrate any positive effect of premedication in patients using LONIC [12]. It is unclear why adverse reactions in LONIC would necessarily follow the same mechanisms as HOIC. It is possible that the high-osmolarity of older contrast media was instrumental in the adverse reactions, a quality that is removed in LONIC. Despite this, many articles in the literature seem to cite studies on premedication while using HOIC as evidence for the efficacy of premedication in improving the safety profile of LONIC.

Currently, LONIC is primarily used by most hospitals. Data regarding the efficacy of premedication of patients at risk for a mild repeat reaction (the greatest risk factor being a previous mild adverse reaction to contrast) is mixed. There is no data currently available that demonstrates an appreciable effect of premedication in preventing the rate or severity of severe adverse reactions or severe repeat/breakthrough adverse reactions when using LONIC. Furthermore, all studies in the current literature discuss the fact that patients who are premedicated may experience an adverse breakthrough reaction of any severity, though the severity is generally in the same severity index as a prior adverse reaction.

Based on available evidence, the following conclusions/recommendations can be considered regarding LONIC and premedication protocols:

(1) There is some data to suggest that premedication may be useful if the goal is to prevent repeat mild adverse reaction in a patient. If the study is not urgent, and if there are no contraindications to the premedication protocol (e.g. severe hypertension, diabetes, fungal infection), the patient can be premedicated after a discussion of the risks and benefits. If the study is urgent, one of the proposed emergent premedication protocols should be considered when possible, though the treating team should be aware of the possibility of a repeat mild and less likely but still possible moderate or severe repeat adverse reaction. It is recognized that in cases of unusual urgency the need for immediate imaging may entirely prevent premedication, and again the clinical team should be prepared for ensuing reaction.

(2) There is no data to suggest that premedication is useful in mitigating the severity or preventing the occurrence of a moderate or severe adverse reaction. This is in part due to the overall rarity of severe adverse reaction to LONIC, making it very difficult to produce a study with enough power to demonstrate a statistical effect of premedication on mitigating future

severe adverse reactions. One of the more powerful studies by Katayama, analyzing almost 170,000 patients, concluded that premedication had no benefit on the adverse reaction profile for patients receiving LONIC. Furthermore, even with premedication, the possibility of a severe breakthrough reaction still exists. Therefore, premedication should not be considered useful for preventing repeat severe adverse reactions in patients with prior severe adverse reactions.

(3) Patients who are at the greatest risk for a severe adverse reaction to LONIC are those who have had a prior severe adverse reaction to LONIC, since repeat reactions tend to be within the same severity index [13, 23]. It is unclear if other risk factors (asthma, general atopy, allergies to medication, allergies to food) can accurately predict future severe reactions [23]. The candidate "at-risk" patients and their treating team should be aware of the risks of a repeat severe adverse reaction in patients with prior severe adverse reaction, and both parties should be encouraged to use alternative imaging modalities. In the case where it is absolutely necessary to perform a study with intravenous LONIC, premedication does not provide any benefit and can be forgone. The patient and treating team must agree that the benefits of the study outweigh the risk of a repeat severe adverse reaction to LONIC. A member of the ordering and/or treating team should be present during injection of intravenous contrast to best assist the radiologists, technicians, and nursing staff in the event of a severe adverse reaction.

Future Goals:

This report is preliminary. Continued review may help to integrate results from additional literature. Subsequentreview may help to address the following points: (1) do other risk factors aside from a prior reaction reliably predict the likelihood of a new adverse reaction; (2) are there additional articles that are relevant to any of the above points; (3) specifically, do any articles offer further clarity on LONIC premedication and its effects on mild adverse reactions; (4) is there developing consensus among practices of other academic hospitals, and for those that have defined their own policies have they noticed differences in numbers of adverse reactions over a long period of time.

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