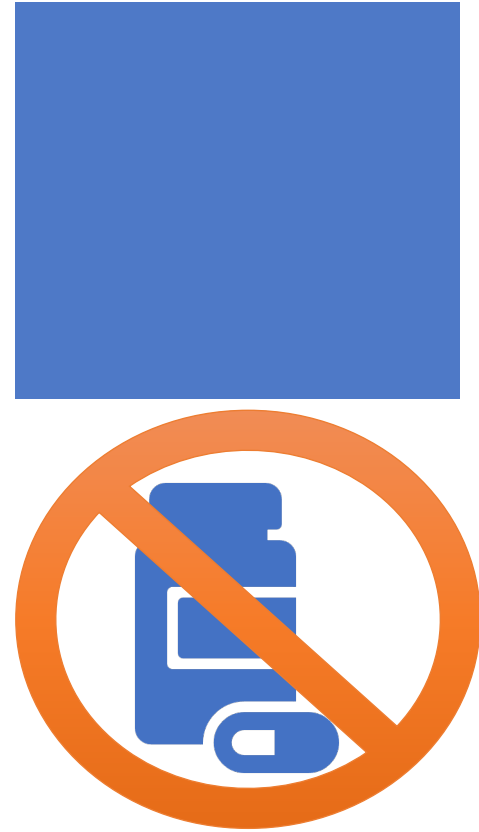


Personalized medicine:

Patients should not receive routine pre-medications to prevent recurrent contrast reactions



Fernanda D. Young, MD

AAIFNC Spring Journal Club

12 May 2021

Disclosures

I have no relevant financial relationships to disclose.

Case:

67yo woman undergoing evaluation for a PE

Med team calls: pt reports acute onset pleuritic chest pain

recent travel, COVID-19 negative

PMH: T2DM with fair control, chronic urinary retention

Allergies: iodine listed, no further details

Team calls you and asks if safe to do the CT PA protocol

What do you do?





Use the right tool at
the right time for
the right reason

*Precision
medicine:*

preventing
contrast
reactions
without pre-
meds

1. 2020 consensus guidelines recommend against routine pre-medication
2. Many contrast reactions are not allergic
3. Switching contrast groups alone reduces reactions
4. Skin testing identifies safe alternative contrast agents
5. Pre-meds cause harm

1. Our guidelines do not recommend pre-meds

- Our 2020 anaphylaxis practice parameters:

“Evidence is lacking to support the role of antihistamines and/or glucocorticoid routine premedication in patients receiving *low or iso-osmolar contrast* material to prevent recurrent radiocontrast media anaphylaxis.”

2. Not all contrast reactions are allergic 🕵️

- What was the reaction?
- When was the reaction? (before 1990, very different agents were used that were often HIGH osmolarity)



Non-allergic
reactions may
not benefit
from pre-meds

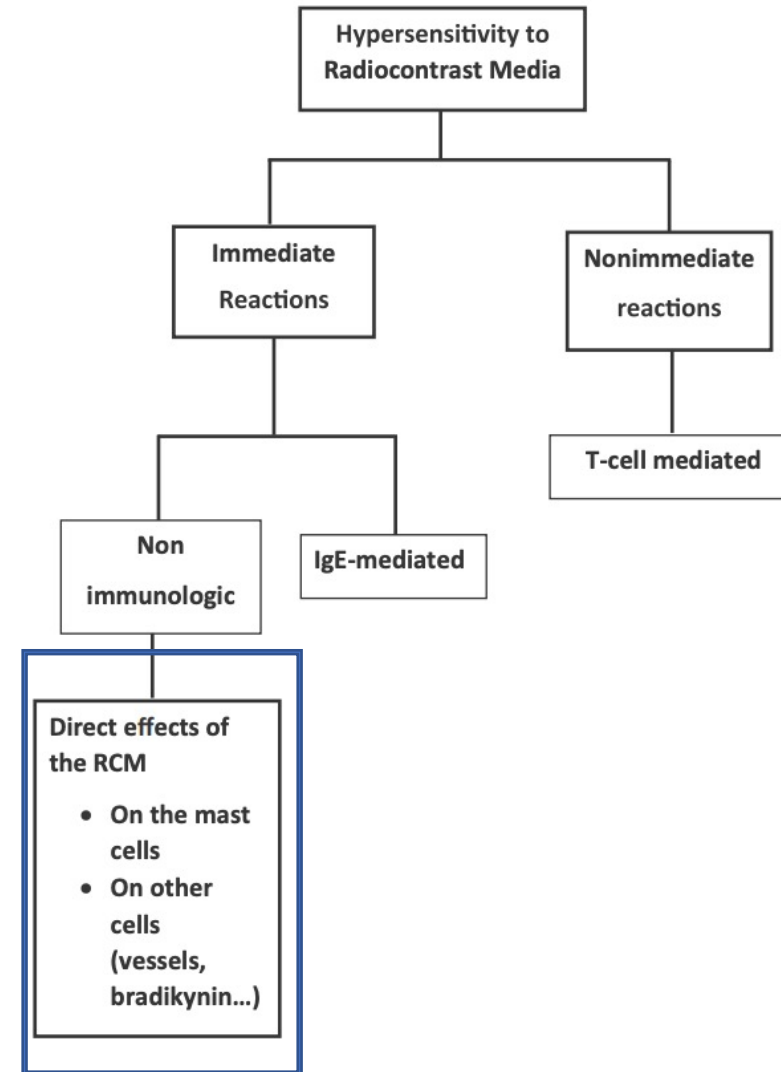
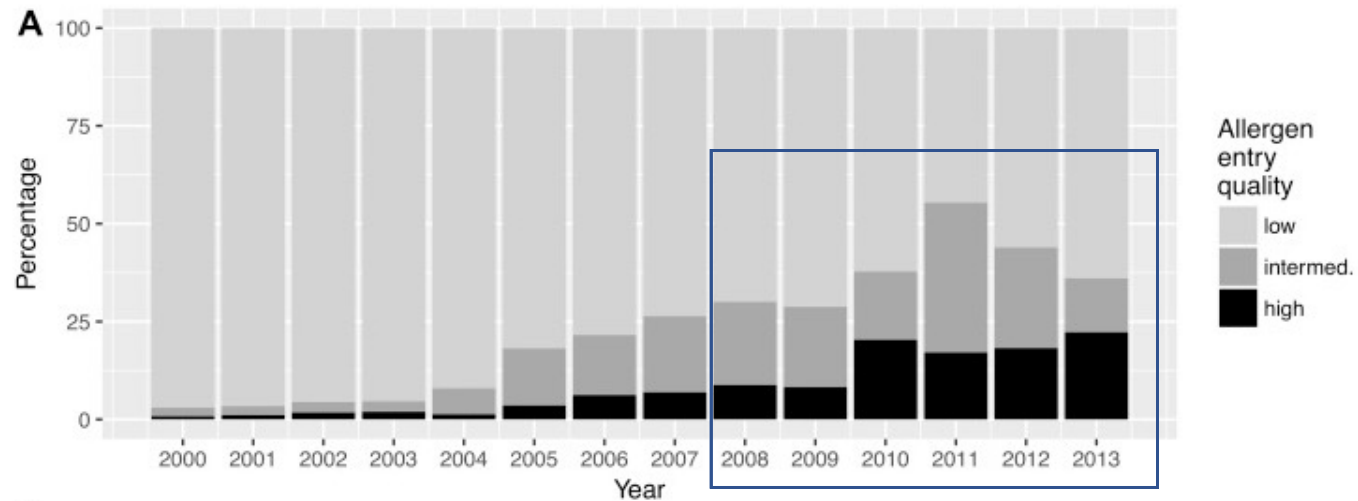


FIGURE 1. Mechanisms of hypersensitivity reactions to radiocontrast media. *RCM*, Radiocontrast media.

Accurate allergen entry helps us help our patients 🖋️



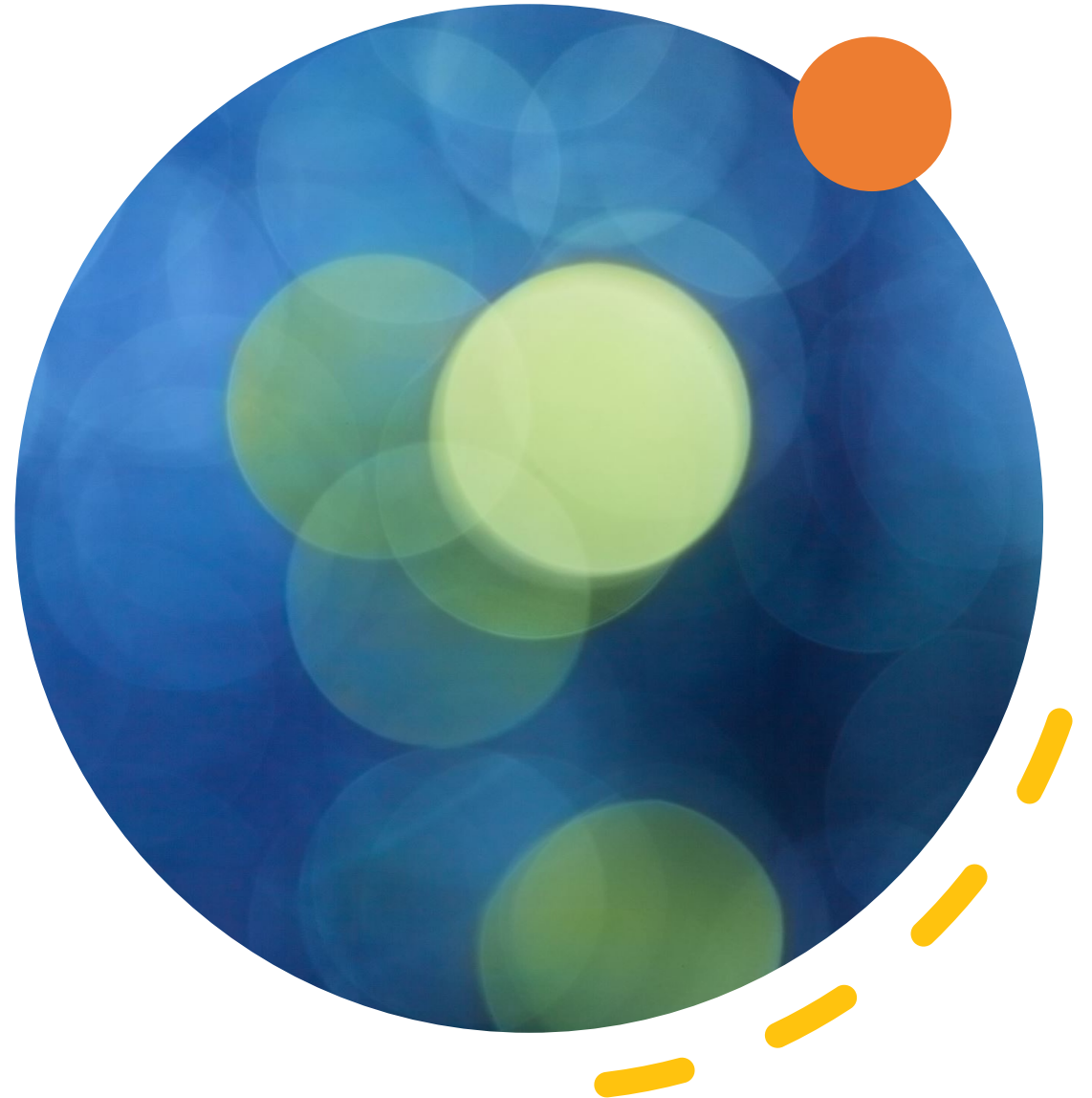
Back to our case

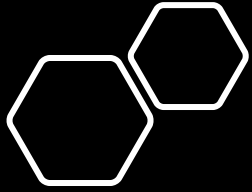


Our patient is tachypneic; she states that 35 years ago she received contrast. She felt warm and had a rash afterward. She has avoided iodine contrast since.

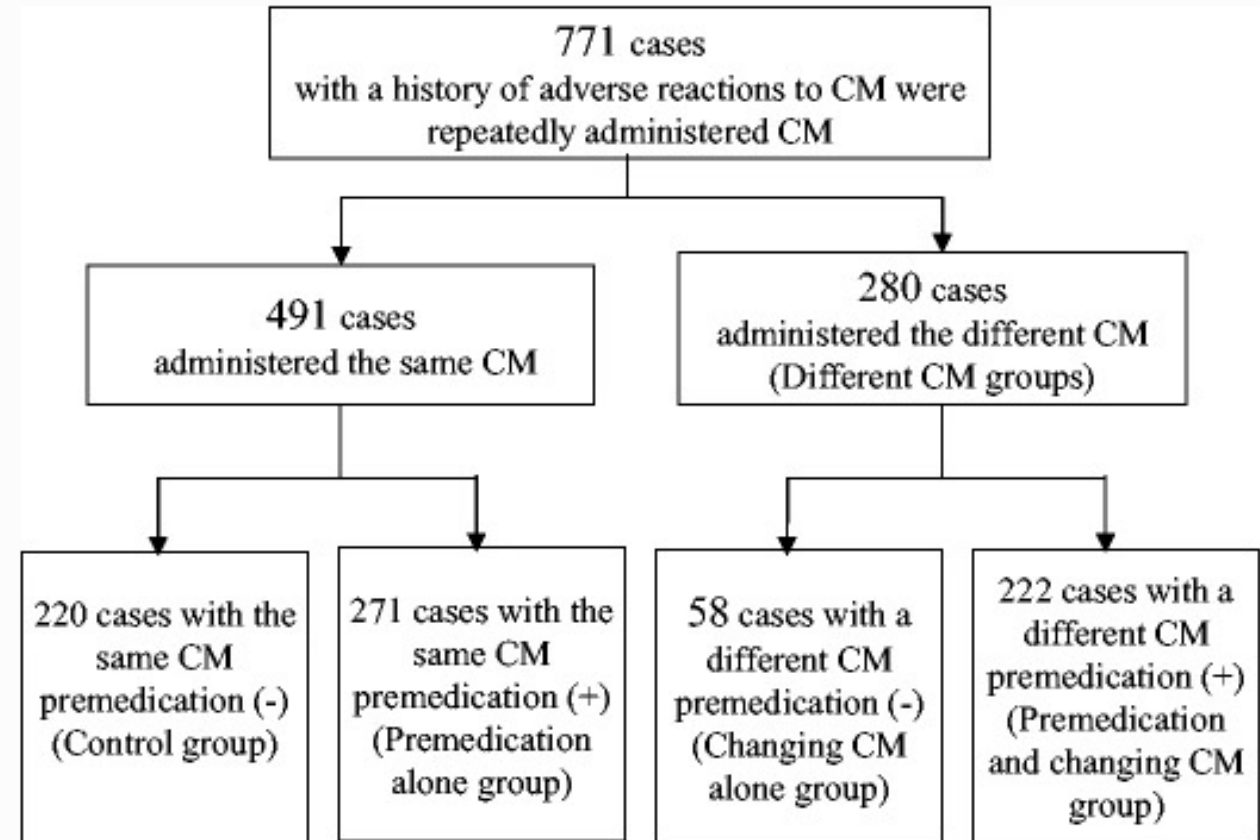


The team is waiting on your recommendation for the CT PA...

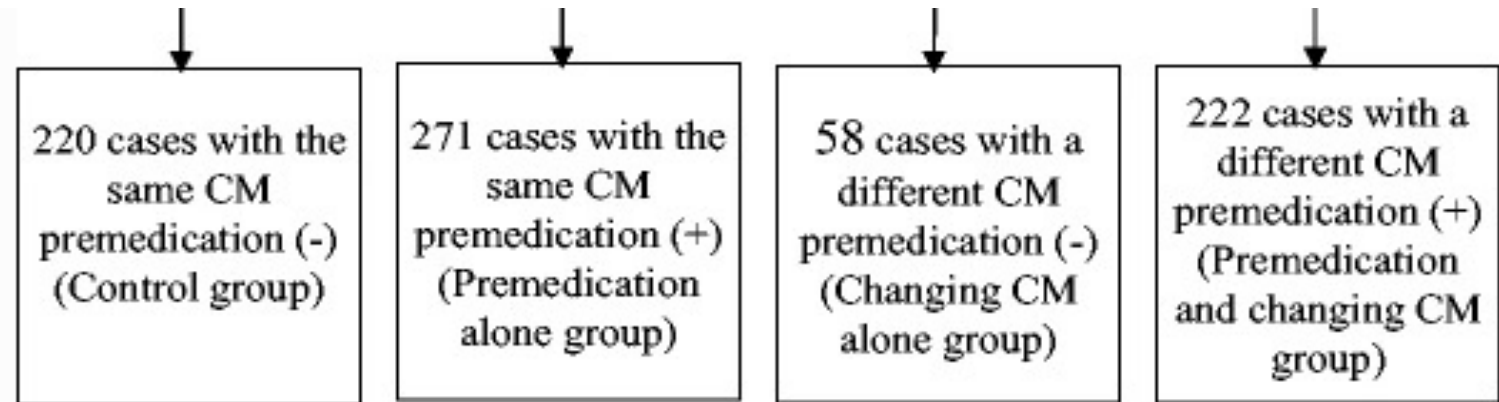




3. Using an alternative contrast medium (CM) decreases reactions



Changing the contrast agent alone reduces reactions!



Total reactions	Non-risk group	Control group	Premedication alone group	Changing CM alone group	Premedication and changing CM group
	576/59057 (1.0%)	61/220 (27.7%)	47/ 271 (17.3%) <i>p=0.006*</i>	3/58(5.2%) <i>p=0.0003*</i>	6/222 (2.7%)
Grade 3	8	1	1	0	0
Grade 2	18	3	1	0	1
Grade 1	307	43	43	1	4
Grade 0	243	14	2	2	1
Total of Grade 1-3	333 (0.6%)	47 (21.4%)	45 (16.7%)	1 (1.7%)	5 (2.2%)

High osmolar contrast is harmful (and outdated)

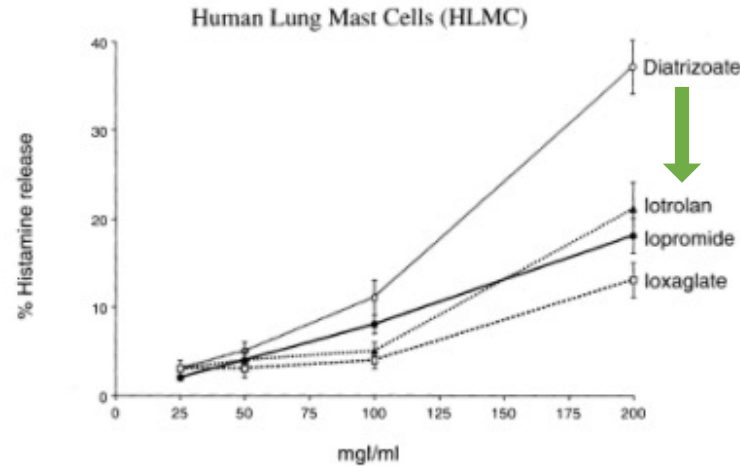


Figure 2. The effects of different doses of RCM on histamine release from HLMC (90 min exposure). A dose dependent response is shown with all four types of RCM. Diatrizoate induced the largest levels of histamine release. No significant difference was observed amongst the other RCM.

High-osmolar
contrast
causes
reactions

Table 4. Severe Symptoms after the Administration of Contrast Material.*

SYMPTOM	HIGH-OSMOLALITY GROUP	NONIONIC GROUP	P VALUE	RELATIVE RISK (95% CI)
	<i>no. (%) of patients</i>			
Warmth	527 (71.5)	443 (58.8)	<0.0001	1.2 (1.1–1.3)
Pain	79 (10.7)	34 (4.5)	<0.0001	2.4 (1.6–3.5)
Chest tightness	75 (10.2)	32 (4.2)	<0.0001	2.4 (1.6–3.6)
Nausea	79 (10.7)	26 (3.5)	<0.0001	3.1 (2.0–4.8)
Vomiting	13 (1.8)	11 (1.5)	NS	1.2 (0.5–2.7)
Dyspnea	17 (2.3)	12 (1.6)	NS	1.4 (0.7–3.0)

*CI denotes confidence interval, and NS not significant.

Low-osmolar contrast has replaced high osmolar contrast

Figure 1 of 1

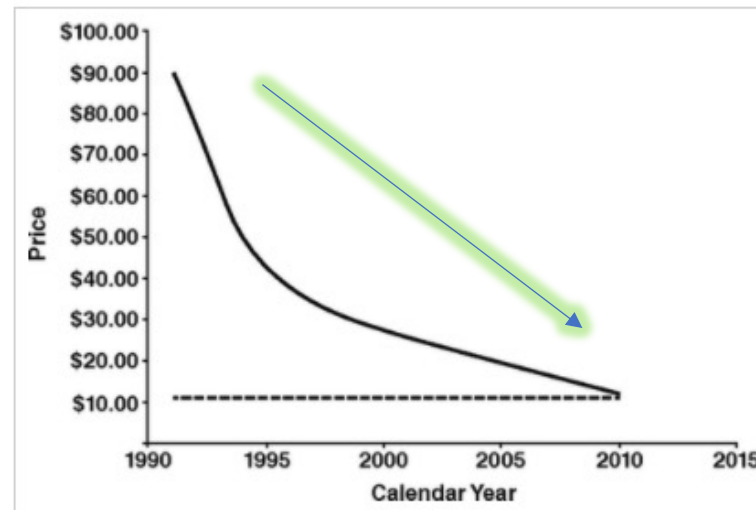
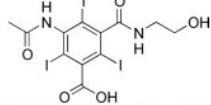
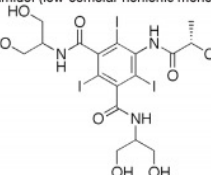
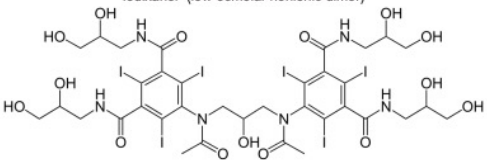
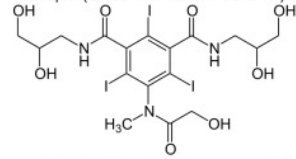
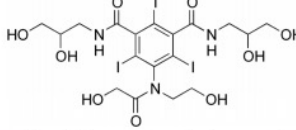
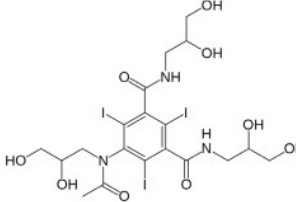
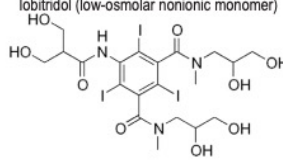
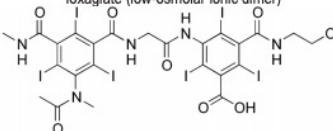
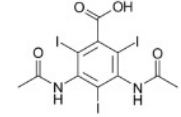


Fig. 1 —Price of highosmolar (*dashed line*) versus low-osmolar (*solid line*) contrast agents from 1991 to present. Price is shown in terms U.S. dollars per dose of contrast agent.

[View larger image](#)

Specificity
matters:
make the
change! 🩺

Table 2. Noncross-reacting radiocontrast agent groups for presumed T-cell-mediated, delayed-onset reactions	
Group	Radiocontrast material
Group A	
	Ioxitalamate (high-osmolar ionic monomer) 
	Iopamidol (low-osmolar nonionic monomer) 
	Iodixanol ^a (low-osmolar nonionic dimer) 
	Iomeprol (low-osmolar nonionic monomer) 
	Ioversol (low-osmolar nonionic monomer) 
	Iohexol ^a (low-osmolar nonionic monomer) 
Group B	
	Iobitridol (low-osmolar nonionic monomer) 
	Ioxaglate (low-osmolar ionic dimer) 
Group C	
	Amidotrizoate/diatrizoate (high-osmolar ionic monomer) 

^a Used in Kaiser Permanente Southern California.



Even knowing approximate year (<1990) is key to assessing risk



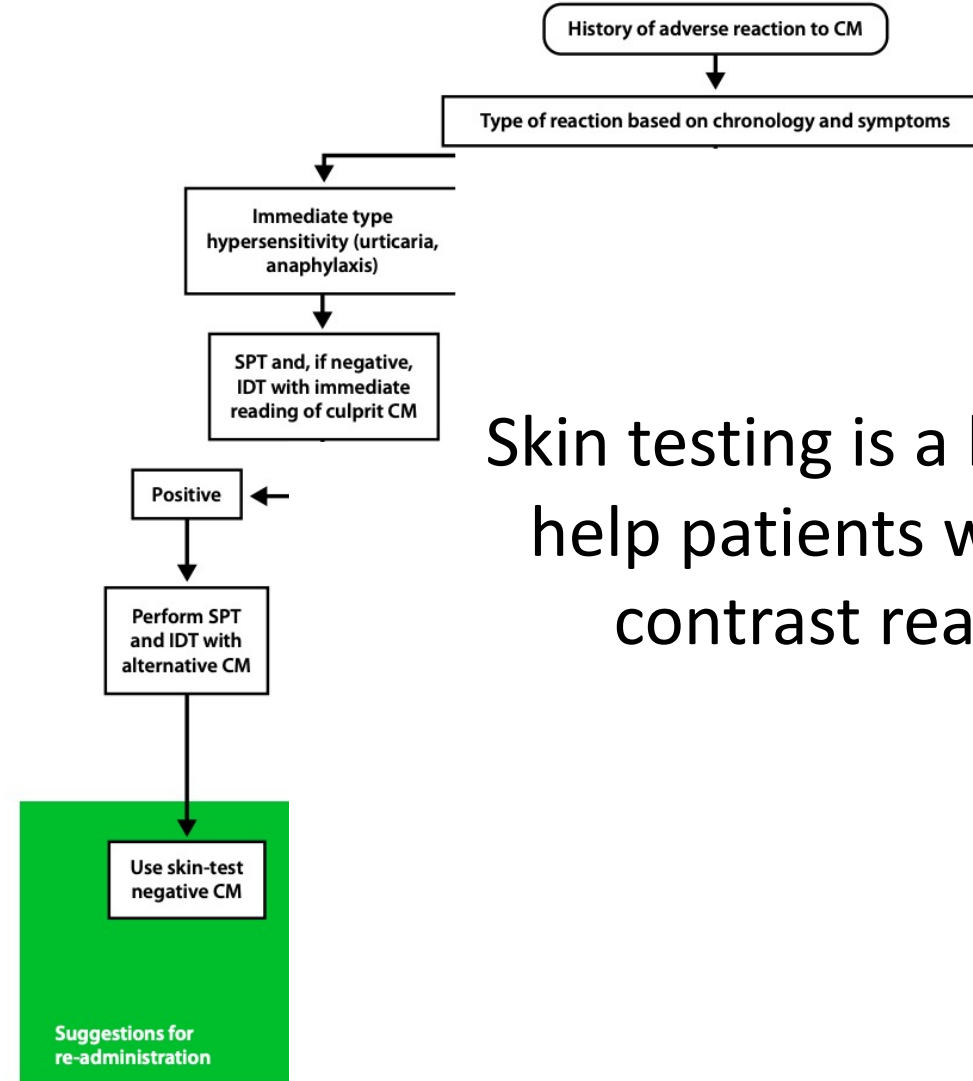
Before 1990, low osmolar agents were too costly for routine use



Knowing that a reaction was before 1990 means being able to safely recommend a low osmolar option (**and significantly reduce risk**)

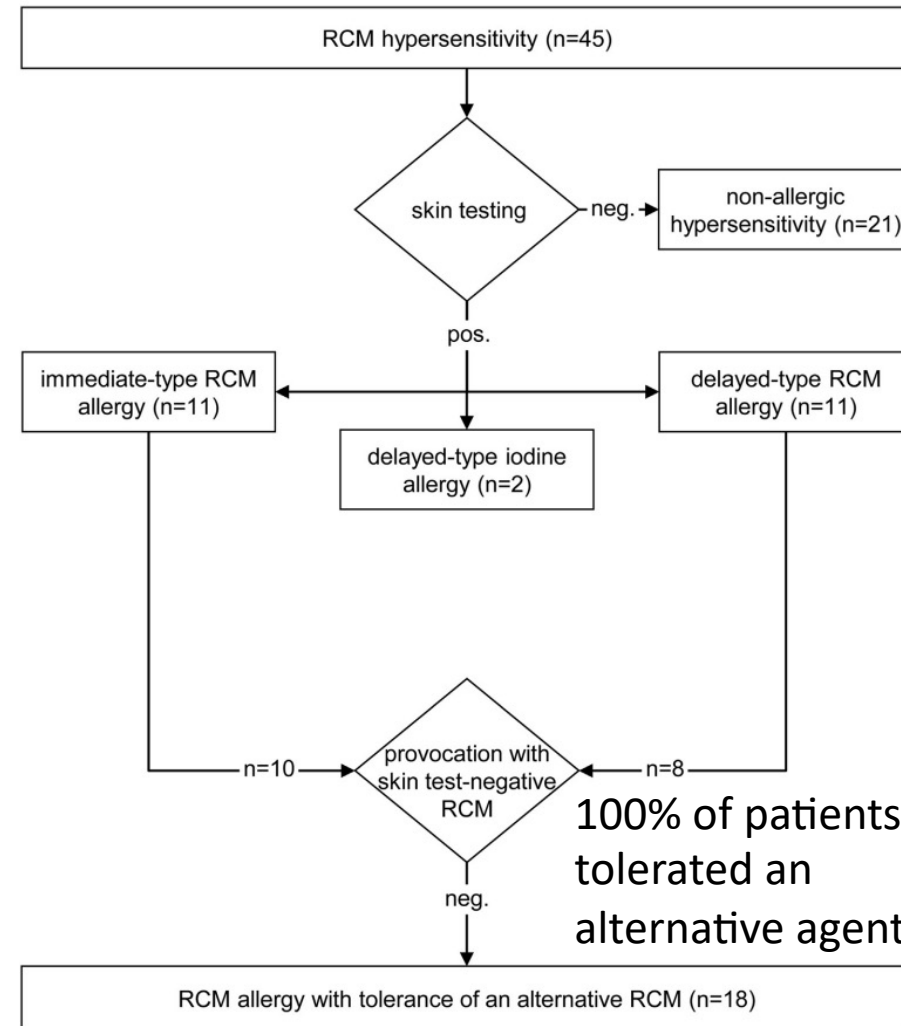
Predicting
future
reactions with
brief history

4. Skin testing is the gold standard 🏆



Skin testing is a key tool to help patients with prior contrast reactions

Skin testing identifies safe alternatives

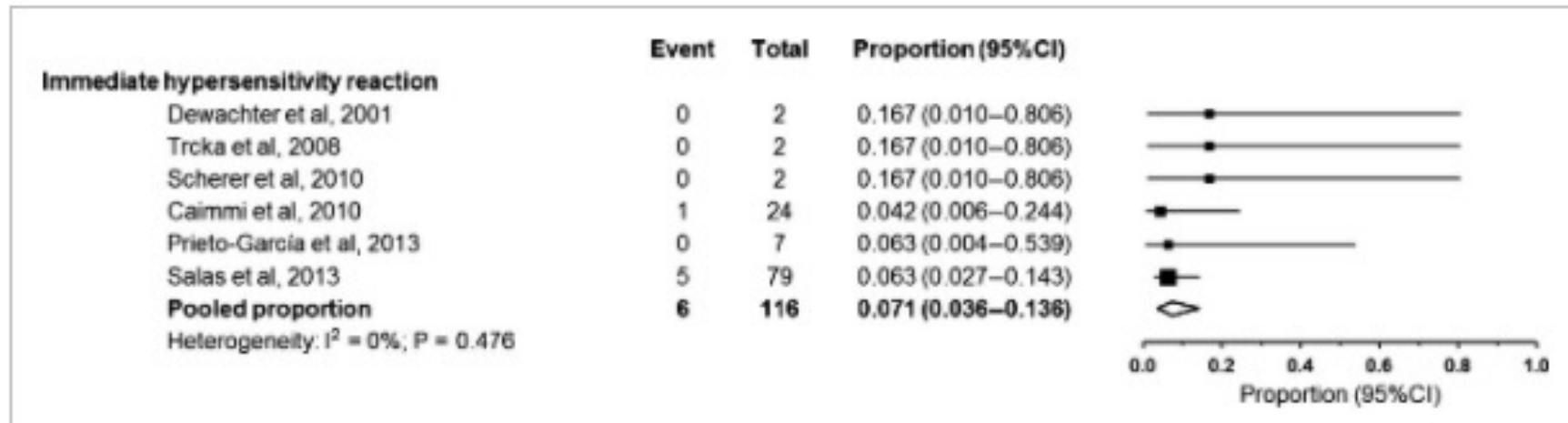


100% of patients
tolerated an
alternative agent!

Skin testing decreases recurrence rates!

Tolerability to skin test-negative ICM

93% did not have recurrence! (95% CI, 4-14%)



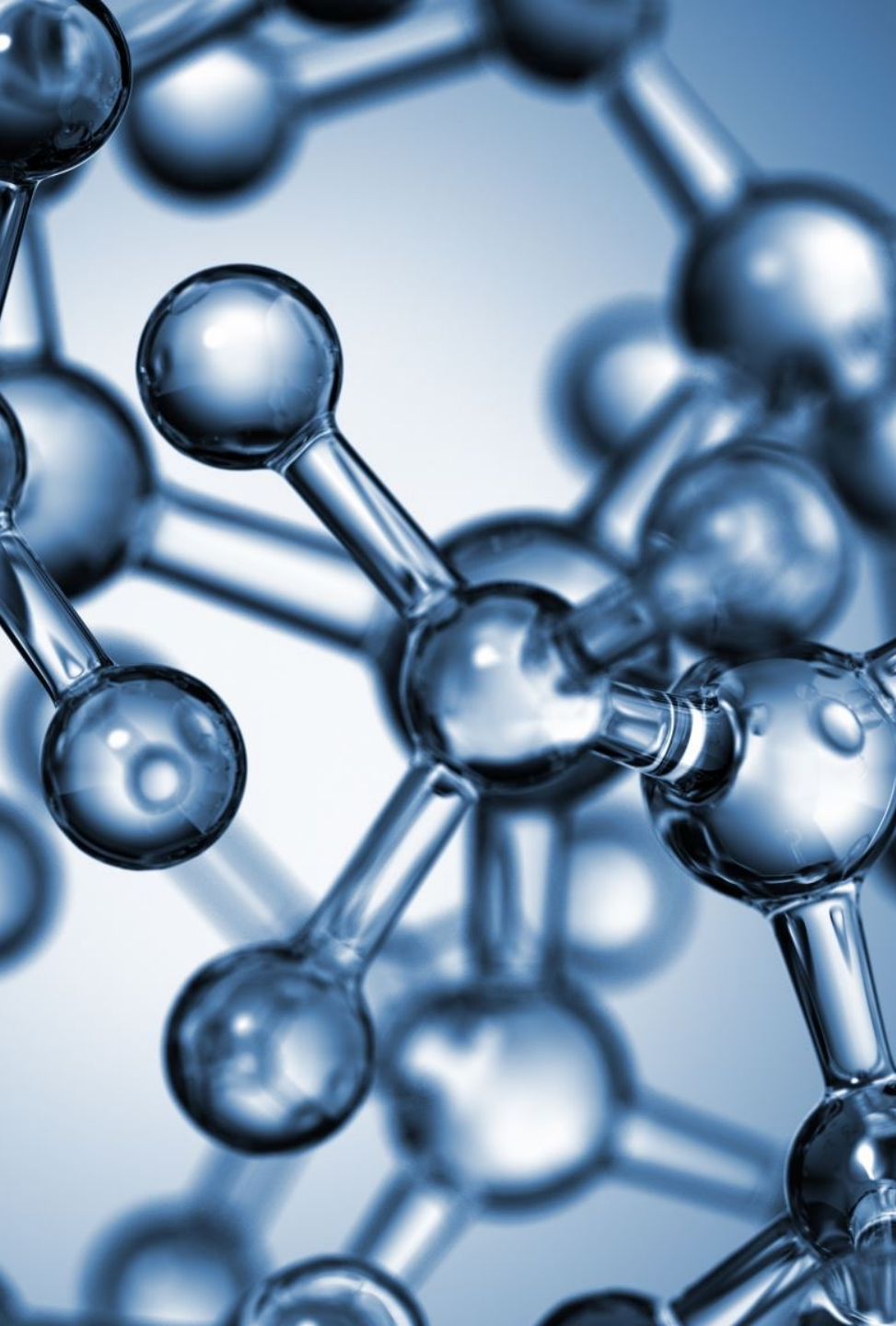
5. Pre-meds cause short-term harm



Table 9
Prevalence of ADRs by Premedication

History of Allergy	Premedication	Cases with Ionic Contrast Media			Cases with Nonionic Contrast Media		
		Total No.	No. with ADR	No. with Severe ADR	Total No.	No. with ADR	No. with Severe ADR
With	With	1,066	368 (34.52)	3 (0.28)	988	139 (14.07)	1 (0.10)
	Without	11,751	2,618 (22.28)	66 (0.56)	13,999	889 (6.35)	14 (0.10)
Without	With	7,694	1,372 (17.83)	28 (0.36)	6,601	315 (4.77)	4 (0.06)
	Without	136,989	15,543 (11.35)	236 (0.17)	133,793	3,539 (2.65)	41 (0.03)

Note.—Percentages in parentheses.



Polypharmacy harms patients

Many patients at risk for contrast reactions have chronic medical conditions

These patients are often older and have impaired metabolism

As such, the data for pre-medications must be convincing to outweigh the risks

- Acute risks of 1st generation anti-histamines like diphenhydramine: *urinary retention, delirium, dizziness, sedation, etc...*
- Acute risks of oral corticosteroids like prednisone: *acute encephalopathy, hyperglycemia, impaired wound healing, nausea, emesis/aspiration, etc...*


Cohorts
were fairly
similar in this
study 

Table 2 Study Population Details

Characteristic	Premedicated Cohort	Control Cohort	PValue
No. of patients	1424	1425	
Female	937 (66)	939 (66)	...
Male	487 (34)	486 (34)	...
Mean age (y)	58	58	...
Year CT performed:			
2008	139 (10)	136 (10)	...
2009	233 (16)	219 (15)	...
2010	263 (18)	246 (17)	...
2011	268 (19)	247 (17)	...
2012	316 (22)	302 (21)	...
2013	205 (14)	272 (19)	...
2014	0 (0)	3 (0.2)	...
Comorbidities			
Coronary artery disease	128 (9)	99 (7)	.05
Congestive heart failure	176 (12)	199 (14)	.23
Peripheral vascular disease	37 (3)	23 (2)	.09
Cerebrovascular disease	49 (3)	63 (4)	.21
Chronic pulmonary disease	143 (10)	139 (10)	.85
Rheumatologic disease	43 (3)	44 (3)	.92
Cirrhosis	36 (3)	28 (2)	.37
Diabetes mellitus	133 (9)	114 (8)	.23
Hemiplegia or paraplegia	12 (0.8)	22 (2)	.12
Chronic kidney disease	166 (12)	141 (10)	.15
Malignancy (any)	80 (6)	94 (7)	.31
Metastatic disease (any)	27 (2)	41 (3)	.11
AIDS/HIV	3 (0.2)	4 (0.3)	>.99

Note.—Unless otherwise indicated, data are number of patients, with percentage in parentheses. AIDS/HIV = acquired immune deficiency syndrome/human immunodeficiency virus infection.

Pre-meds caused harm in inpatients

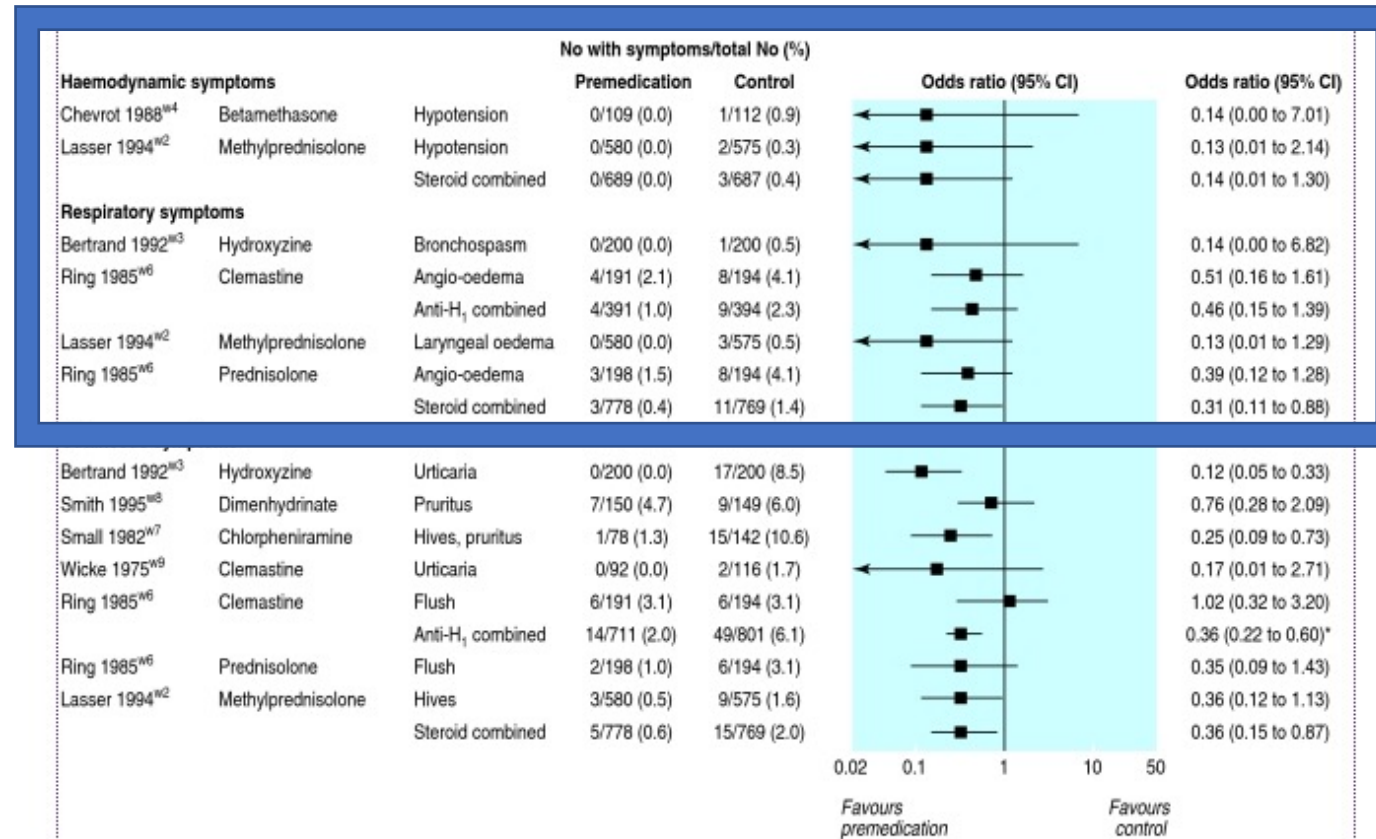
Table 3 Summary of Observed Indirect Harm Associated with Premedication in the Inpatient Study Cohort

Characteristic	Premedicated Cohort	Control Cohort	Difference	PValue
Median Times (h)				
Time to CT	42 (24–106)*	17 (5–61)*	+25	< .001
CT to discharge	87 (36–189)*	95 (49–193)*	–8	.002
Total length of stay	158 (84–312)*	133 (73–262)*	+25	< .001
Mean Times (h)				
Time to CT	108	61	+47 [†]	...
CT to discharge	163	166	–3 [†]	...
Total length of stay	272	226	+46 [†]	...
HAIs (%)	5.1 (72/1424)	3.1 (44/1425)	+2.0	.008
<i>Clostridium difficile</i>	2.7 (38/1424)	1.6 (23/1425)	+1.1	.05
Central-line associated bloodstream infection	1.3 (18/1424)	0.2 (3/1425)	+1.1	< .001
Catheter-associated urinary tract infection	0.6 (8/1424)	0.9 (13/1425)	–0.3	.38
HAIs per 1000 hospital days	4.3	3.3	+1.1%	.17

Note.—Unless otherwise indicated, data are percentages, with proportions in parentheses. HAIs refers to the total number of selected HAIs recorded prospectively during the study period. Some HAIs (eg, ventilator-associated pneumonia) were not recorded prospectively and could not be studied. Some HAIs were not tracked during the entire study period. Therefore, the number of HAIs reported in this table is less than the number that actually occurred.

*Data in parentheses are interquartile ranges.

Pre-meds don't prevent hemodynamic or respiratory reactions



If pre-meds only significantly help hives, is that worth the risk to the patient?

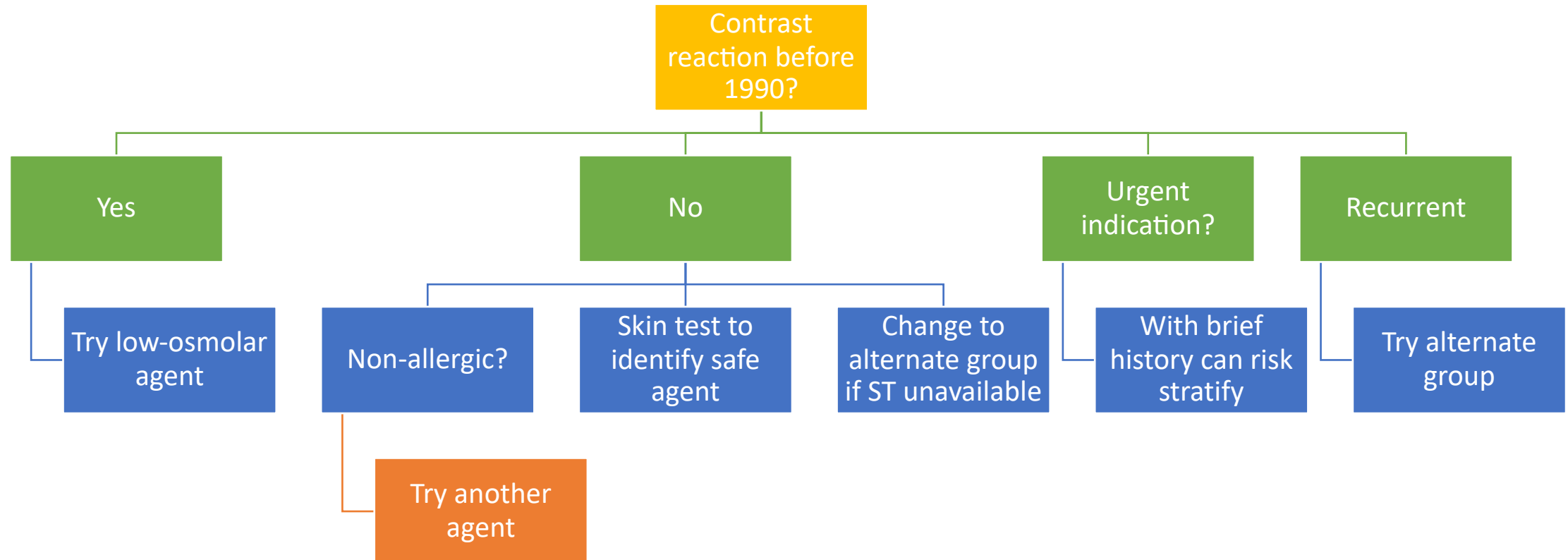
No!



Side effects

Efficacy

A proposed workflow



To recap: 

2020 consensus guidelines recommend **against** *routine* pre-medications

Many contrast reactions are **not** allergic

Switching contrast groups alone **reduces reactions**

Skin testing identifies **safe alternative** contrast agents

Pre-meds cause short-term **harm**

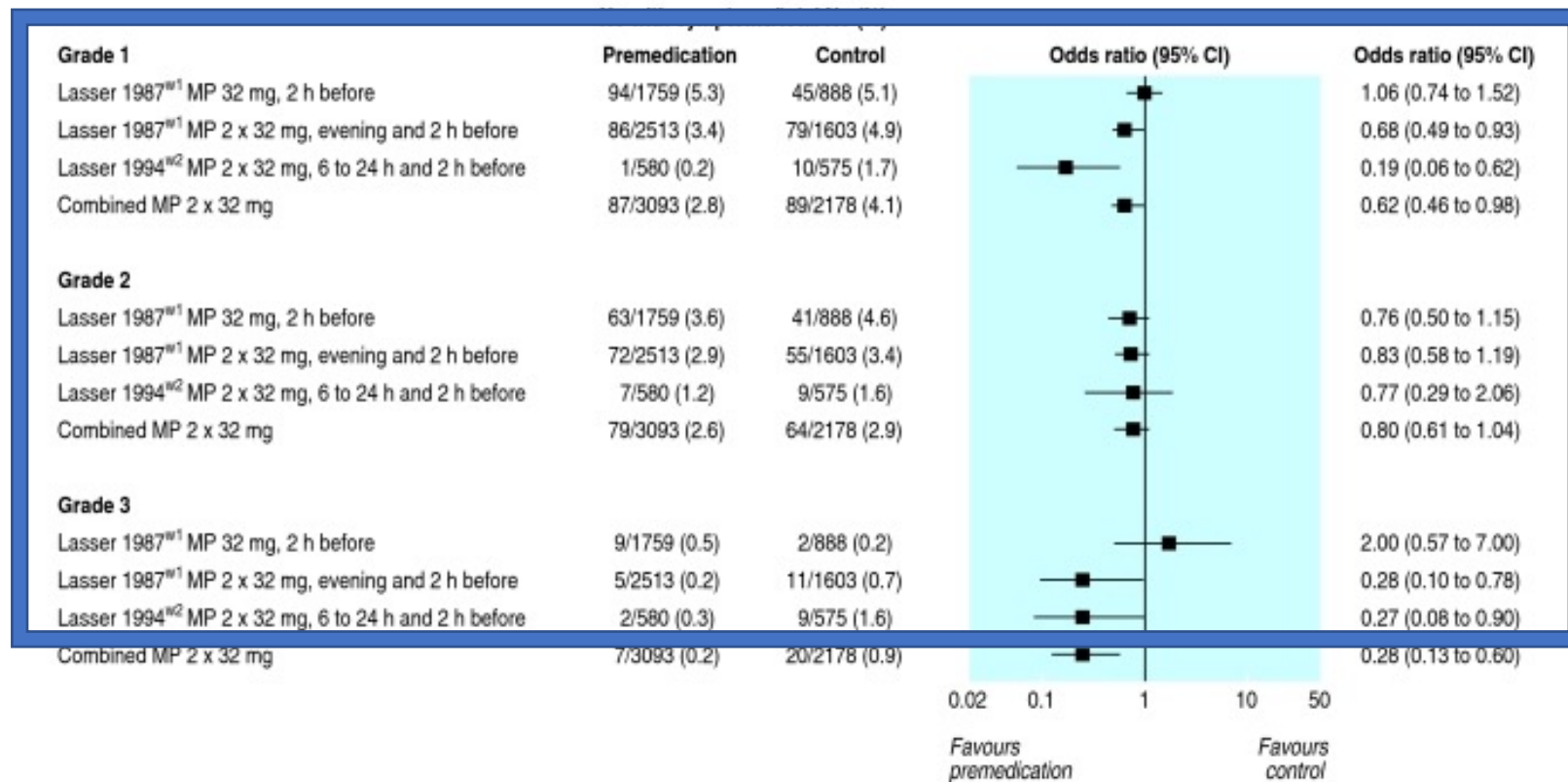
Rebuttal

Pre-meds **do not** always prevent adverse reactions

Pre-meds cause long-term **harms**

Pre-meds *may be used* in specific situations (just not routinely)

1. Most studies do not favor pre-meds 🤯



Consensus guidelines came to same point: pre-meds do not help

1108 SHAKER ET AL

J ALLERGY CLIN IMMUNOL
APRIL 2020

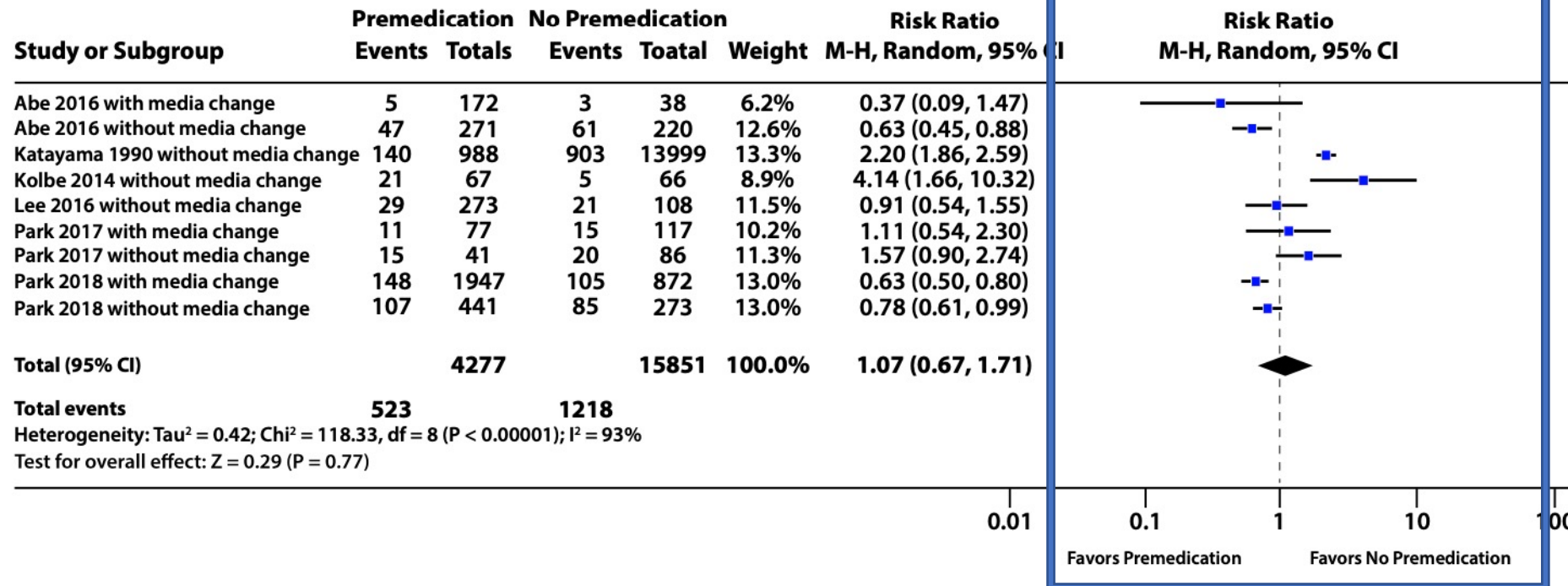


FIG 7. Should antihistamine and/or glucocorticoid premedication be used to prevent recurrent HSRs to RCM?

2. Recurrent contrast pre-meds over time cause harm

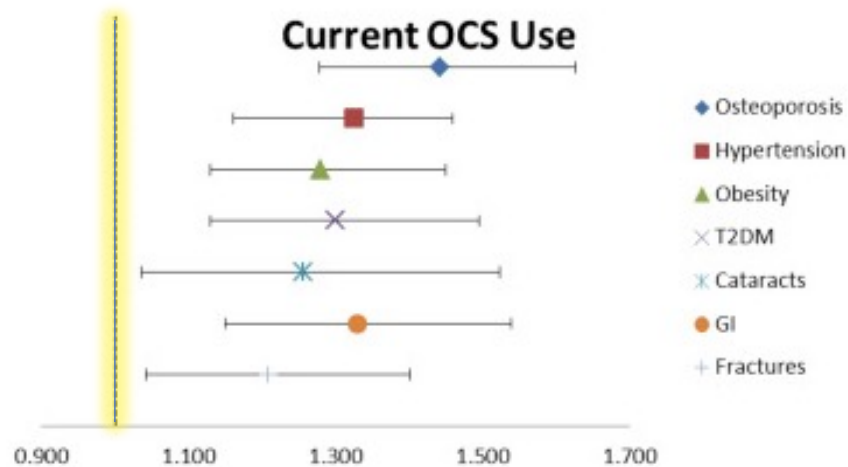


Fig 2 Odds ratio of AEs associated with use of 4 or more prescriptions by condition results of logistic regression controlling for age, sex, geographic region, years since the index date, insurance type, use of immunosuppressive medication (yes/no; not OCS), and general comorbidity burden (NCC). AEs that were not statistically significant are not included: metabolic syndrome, avascular necrosis, dyslipidemia, glaucoma, and tuberculosis.

Dangerous long-term effects of steroids



- “Commonly-cited AEs associated with long-term corticosteroid exposure included **hypertension** (prevalence >30%); **bone fracture** (21%-30%); **cataract** (1%-3%); **nausea, vomiting**, and other **gastrointestinal** conditions (1%-5%); and **metabolic** issues (eg, weight gain, hyperglycemia, and type 2 diabetes; cases had **4-fold** the risk of controls).
- AEs like **peptic ulcer** and **myocardial infarction** are particularly costly to payers (1-year cost of \$21,825 and \$26,472, respectively, in year-2009 USD)”

NNT for severe reactions is too high

- Estimated NNT to *prevent one contrast reaction of any severity* in patients with a previous iodinated contrast reaction is approximately 69 (95% CI, 39–304).
- If only **severe** reactions are considered, the estimated NNT is **much higher** (569 to prevent one severe reaction; 95% CI, 389–1083).
- Given that the minimum proven efficacious duration of oral corticosteroid prophylaxis has been found to be 12 hours, **approximately 285 days of premedication would be required to prevent one serious reaction** (12 hours × 569 regimens).

How did our
67yo patient
do?



Weighed risks/benefits given her T2DM



Given remote history and likely high
osm contrast reaction, received iso-
osmolar contrast without pre-meds



No adverse reactions!



CT PA showed PE and she was started
on therapeutic anti-coagulation

3. Should we ever recommend pre-meds?

Rarely, but this should be personalized and not routine 🙋

Emergent need for
contrast scan 🚑

Patient with prior
acute reactions
despite changing
contrast agent 😓

Otherwise, let us
tailor the agent for
the patient!

Address drug
reactions as part of
ongoing pt
evaluation

Precision medicine:

The right tool at
the right time for
the right reason



1. 2020 consensus guidelines recommend **against** routine pre-medications
2. Many contrast reactions are **not** allergic
3. Switching contrast groups alone **reduces reactions**
4. Skin testing identifies **safe alternative** contrast agents
5. Pre-meds cause **harm**
6. Pre-meds **do not** always prevent adverse reactions
7. Pre-meds cause **worse long-term** outcomes
8. Pre-meds *may help* in specific situations (just not routinely)

Thank you 



References



- Abe S, Fukuda H, Tobe K, Ibukuro K. Protective effect against repeat adverse reactions to iodinated contrast medium: Premedication vs. changing the contrast medium. *Eur Radiol*. 2016 Jul;26(7):2148-54. doi: 10.1007/s00330-015-4028-1. Epub 2015 Oct 1. PMID: 26427700.
- Barrett BJ, Parfrey PS, Vavasour HM, O'Dea F, Kent G, Stone E. A comparison of nonionic, low-osmolality radiocontrast agents with ionic, high-osmolality agents during cardiac catheterization. *N Engl J Med*. 1992 Feb 13;326(7):431-6. doi: 10.1056/NEJM199202133260702. PMID: 1732770.
- Davenport MS, Mervak BM, Ellis JH, Dillman JR, Dunnick NR, Cohan RH. Indirect Cost and Harm Attributable to Oral 13-Hour Inpatient Corticosteroid Prophylaxis before Contrast-enhanced CT. *Radiology*. 2016 May;279(2):492-501. doi: 10.1148/radiol.2015151143. Epub 2015 Nov 4. PMID: 26536404.
- Deng F, Li MD, Wong A, Kowalski LT, Lai KH, Digumarthy SR, Zhou L. Quality of Documentation of Contrast Agent Allergies in Electronic Health Records. *J Am Coll Radiol*. 2019 Aug;16(8):1027-1035. doi: 10.1016/j.jacr.2019.01.027. Epub 2019 Mar 4. PMID: 30846398.
- 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 Jun;175(3):621-8. doi: 10.1148/radiology.175.3.2343107. PMID: 2343107.

References



- Macy EM. Current Epidemiology and Management of Radiocontrast-Associated Acute- and Delayed-Onset Hypersensitivity: A Review of the Literature. *Perm J*. 2018;22:17-072. doi: 10.7812/TPP/17-072. PMID: 29309271; PMCID: PMC5760058.
- Mervak BM, Davenport MS, Ellis JH, Cohan RH. Rates of Breakthrough Reactions in Inpatients at High Risk Receiving Premedication Before Contrast-Enhanced CT. *AJR Am J Roentgenol*. 2015 Jul;205(1):77-84. doi: 10.2214/AJR.14.13810. PMID: 26102383.
- Peachell PT, Morcos SK. Effect of radiographic contrast media on histamine release from human mast cells and basophils. *Br J Radiol*. 1998 Jan;71(841):24-30. doi: 10.1259/bjr.71.841.9534695. PMID: 9534695..
- Sánchez-Borges M, Aberer W, Brockow K, Celik GE, Cernadas J, Greenberger PA, Masse MS, Schrijvers R, Trautmann A. Controversies in Drug Allergy: Radiographic Contrast Media. *J Allergy Clin Immunol Pract*. 2019 Jan;7(1):61-65. doi: 10.1016/j.jaip.2018.06.030. Epub 2018 Dec 17. PMID: 30573421.
- Schönmann C, Brockow K. Adverse reactions during procedures: Hypersensitivity to contrast agents and dyes. *Ann Allergy Asthma Immunol*. 2020 Feb;124(2):156-164. doi: 10.1016/j.anai.2019.11.022. Epub 2019 Nov 22. PMID: 31765812.
- Shaker MS, Wallace DV, Golden DBK, Oppenheimer J, Bernstein JA, Campbell RL, Dinakar C, Ellis A, Greenhawt M, Khan DA, Lang DM, Lang ES, Lieberman JA, Portnoy J, Rank MA, Stukus DR, Wang J; Collaborators, Riblet N, Bobrownicki AMP, Bontrager T, Dusin J, Foley J, Frederick B, Fregene E, Hellerstedt S, Hassan F, Hess K, Horner C, Huntington K, Kasireddy P, Keeler D, Kim B, Lieberman P, Lindhorst E, McEnany F, Milbank J, Murphy H, Pando O, Patel AK, Ratliff N, Rhodes R, Robertson K, Scott H, Snell A, Sullivan R, Trivedi V, Wickham A; Chief Editors, Shaker MS, Wallace DV; Workgroup Contributors, Shaker MS, Wallace DV, Bernstein JA, Campbell RL, Dinakar C, Ellis A, Golden DBK, Greenhawt M, Lieberman JA, Rank MA, Stukus DR, Wang J; Joint Task Force on Practice Parameters Reviewers, Shaker MS, Wallace DV, Golden DBK, Bernstein JA, Dinakar C, Ellis A, Greenhawt M, Horner C, Khan DA, Lieberman JA, Oppenheimer J, Rank MA, Shaker MS, Stukus DR, Wang J. Anaphylaxis-a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. *J Allergy Clin Immunol*. 2020 Apr;145(4):1082-1123. doi: 10.1016/j.jaci.2020.01.017. Epub 2020 Jan 28. PMID: 32001253.

References



- Sullivan PW, Ghushchyan VH, Globe G, Schatz M. Oral corticosteroid exposure and adverse effects in asthmatic patients. *J Allergy Clin Immunol*. 2018 Jan;141(1):110-116.e7. doi: 10.1016/j.jaci.2017.04.009. Epub 2017 Apr 27. PMID: 28456623.
- Tramèr MR, von Elm E, Loubeyre P, Hauser C. Pharmacological prevention of serious anaphylactic reactions due to iodinated contrast media: systematic review. *BMJ*. 2006 Sep 30;333(7570):675. doi: 10.1136/bmj.38905.634132.AE. Epub 2006 Jul 31. PMID: 16880193; PMCID: PMC1584363.
- Trautmann A, Brockow K, Behle V, Stoevesandt J. Radiocontrast Media Hypersensitivity: Skin Testing Differentiates Allergy From Nonallergic Reactions and Identifies a Safe Alternative as Proven by Intravenous Provocation. *J Allergy Clin Immunol Pract*. 2019 Sep-Oct;7(7):2218-2224. doi: 10.1016/j.jaip.2019.04.005. Epub 2019 Apr 10. PMID: 30980898.
- Wilmot A, Mehta N, Jha S. The adoption of low-osmolar contrast agents in the United States: historical analysis of health policy and clinical practice. *AJR Am J Roentgenol*. 2012 Nov;199(5):1049-53. doi: 10.2214/AJR.11.8426. PMID: 23096178.
- Yoon SH, Lee SY, Kang HR, Kim JY, Hahn S, Park CM, Chang YS, Goo JM, Cho SH. Skin tests in patients with hypersensitivity reaction to iodinated contrast media: a meta-analysis. *Allergy*. 2015 Jun;70(6):625-37. doi: 10.1111/all.12589. Epub 2015 Mar 20. PMID: 25649510.