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## **Computerized Tomography for Nontraumatic Abdominal Pain in the Emergency Department: Evidence-Based Answers to Ten Common Questions**

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In the space of a few short years, we have become dependent on computerized tomography (CT) as an essential tool in the evaluation of abdominal pain. We've taken for granted the usefulness of this apparatus, but there are some questions that seem near-universal among physicians ordering studies, and other questions that need to be answered every academic year. Just as with other areas of medicine, there is a lot of mythology and bad science behind much of the information surrounding CT. The questions that I find myself thinking about most frequently are these:

- 1) How serious is the risk of increased cancer occurrence after CT?
- 2) What do I tell a pregnant woman about the risk of receiving an abdominal CT?
- 3) How important is oral contrast material to the accuracy of the study, and how long does it really take to reach its intended target?
- 4) How important is intravenous contrast material to the accuracy of the study?
- 5) What is the connection between seafood/shellfish allergy and intravenous contrast material, and how much should I worry about it?
- 6) If patients say they are allergic to intravenous contrast, can't we just give them some diphenhydramine and steroids before they're injected?
- 7) What about the patient with a history of asthma – does that really increase the risk of anaphylaxis?
- 8) Do we need a creatinine on everyone before performing contrast studies?
- 9) Can we prevent contrast-induced nephropathy (CIN) by prepping the patient with n-acetylcysteine/theophylline/mannitol/bicarbonate/other interventions?
- 10) What are the facts about the patient who takes metformin and needs a study requiring intravenous contrast?

I set out to answer these questions in the course of this article.

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### **Question 1: How serious is the risk of increased cancer occurrence after CT?**

Aside from the issues of contrast allergy and contrast-induced nephropathy, the biggest worries are almost certainly radiation exposure and the future risk of cancer. A 2001 article by Brenner and Elleson (1) in the *American Journal of Radiology* examined this subject in the pediatric population. Using standard models that assumed a linear extrapolation of risks from medium to low doses, they estimated the lifetime cancer mortality risks attributable to radiation exposure for an abdominal scan in a 1-year-old to be 0.18%. In other words, of the approximately 600,000 children under the age of 15 years who receive an abdominal CT annually, about 500 might eventually die from cancer attributable to the CT radiation. The authors also recognize that the risk-benefit balance is still strongly tilted toward benefit.

On the other hand, two large studies looked at cancer incidence and mortality many years after cardiac catheterization procedures in children; neither study reported an increase in cancer occurrence at remote follow-up years later (2,3). The estimated radiation dose from a cardiac catheterization is 200 to 500 mGray (mGy), whereas the estimated dose received from a single full-body CT examination in a child is 14 – 21 mGy. The only adverse effects statistically proven at the dose levels associated with diagnostic radiation procedures is a very small increase in childhood malignancy, with an estimated increase of one additional cancer death per 1700 exposures of 10 mGy.

Applying these estimates to adults, Brenner and Elleson determined that a single full-body CT examination in a 45-year-old adult would result in an estimated lifetime cancer mortality risk of around 0.08% (4). They also note that a 45-year-old adult who plans to submit himself to annual full-body screening CT examinations up to age 75 (30 examinations) would amass an overall estimated lifetime risk of cancer mortality of about 1.9%, or 1 in 50.

**Conclusion:** Yes, there is a slight risk of increased cancer occurrence after diagnostic CT scans: the younger the patient and the greater the dose of ionizing radiation, the greater the risk. Parents of children receiving diagnostic radiographic studies need to know that the potential risk of a 1 year-old developing cancer sometime during life after a single CT is about 1 in 500. If this risk appears to outweigh the potential benefit, an alternative diagnostic study should be sought. In adult patients, the increased risk is minimal – certainly less than one in 1000. The older the patient, the lower the lifetime risk, but effects are cumulative over time.

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### **Question 2: What do I tell a pregnant woman about the risk of receiving an abdominal CT scan?**

At baseline, a pregnant woman has a 15% chance of spontaneous abortion, a 3% risk for major malformation, and a 4% possibility of restricted fetal growth (5). The teratogenicity of radiation is dose-dependent, and radiation exposures greater than 500 mGy cause fetal damage. The most vulnerable period for radiation-induced central nervous system damage is 8 – 15 weeks after conception. The estimated fetal exposure for an abdominal CT scan is 30 mGy (6). Exposure to less than 50 mGy has not been shown to be associated with differences in pregnancy outcomes when compared with a control population who received only background radiation (usually less than 1 mGy) during the 9 months of gestation (7).

**Conclusion:** There is no risk to a fetus if a pregnant woman requires a single abdominal CT scan.

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### **Question 3: How important is oral contrast material to the accuracy of an abdominal CT, and how long does it really take to reach its intended target?**

Although CT is a relatively recent technology, there have been giant strides made in the equipment and what once was gospel may no longer be so. The early slow "Step and Scan" machines required long image acquisition times, meaning the chance for movement artifact from respirations and bowel peristalsis was high. To maximize imaging accuracy, it was necessary to give high volume oral contrast to opacify the small bowel; there were few studies comparing oral contrast with no oral contrast, as the cost of contrast material itself is low and there were no direct adverse events for the patient.

The patient must wait for 60 to 90 minutes after drinking a contrast agent before it is adequately distributed in the bowel. Studies have shown that by requiring oral contrast, the patient's stay in the ED is extended by far more than 90 minutes. In one study, there was 173-minute increase in time from registration to disposition in patients who received oral contrast prior to CT versus those who didn't – an 83-minute extension of the 90-minute total bowel opacification time (8).

CT technology has evolved, and image acquisition with newer helical technology has practically eliminated movement due to respiration and peristalsis (9). Many radiologists who read these scans now feel very comfortable interpreting them without oral contrast and the literature supports their practice. Inflammatory conditions often manifest with abnormalities in the fat of the peritoneal cavity and omentum, which should be detectable without oral contrast. Abscesses are also detected without oral contrast. Bowel wall pathology may be better interpreted with bowel distention, but oral contrast does not distend the colon, and the detection of pneumatosis should not be improved by oral contrast.

In fact, recent studies indicate that oral contrast adds very little to the accurate diagnosis of nontraumatic abdominal pain. Lee et al. did a prospective study of 100 Emergency Department patients with abdominal pain who were scanned initially without oral contrast, and again 90 minutes after oral contrast with identical scanning parameters (10). Experienced radiologists were given no information about medical history before they interpreted the noncontrast scans; the same group of radiologists interpreted scans performed after ingestion of oral contrast, but did not have access to earlier matched scans or interpretations of those scans. At first glance the results are terribly impressive: for 21 patients there was clinically significant disagreement between contrast and noncontrast interpretations – 11 had normal noncontrast but abnormal contrast studies, six had abnormal noncontrast studies but normal contrast studies, and four had abnormal studies with and without contrast, but a disagreement in the abnormality by the interpreting radiologist. However on careful *post hoc* analysis, only two cases were discrepant primarily because of the addition of oral contrast; 18 were due solely to interobserver variability (one turned out not to be discrepant). This 18% interobserver variability is not significantly different from other published studies, which show discrepancy rates of up to 38% (11). There is also the ever-present problem of self-referential bias – that is, the final diagnosis is that given by the interpretation of the CT scan.

When looking at the accuracy of abdominal CT with and without contrast when specifically looking for appendicitis, the results are surprising. A meta-analysis of 23 studies showed that unenhanced CT sensitivity was similar (95% vs. 92%) as was specificity (97% vs. 94%) and accuracy (97% vs. 89%) (12).

**Conclusion:** Oral contrast takes at least 90 minutes to adequately opacify the bowel and increases length of stay in the Emergency Department by almost double that amount of time, but adds little if anything to the accuracy of diagnosis in patients with nontraumatic abdominal pain. Your local radiologist, however, may not

be comfortable interpreting CT scans without the contrast and might have the final say. Discuss this controversy with your radiologists to reach an agreement that satisfies everyone.

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#### **Question 4: How important is intravenous contrast material to the accuracy of the study?**

Much like oral contrast, intravenous contrast has become accepted as a routine part of the CT evaluation for nontraumatic abdominal pain without a great deal of evidence indicating that it is helpful, but with the additional potential downside of adverse reactions and long-term complications.

Many authors have recommended use of intravenous contrast with CT scanning in the evaluation of undifferentiated nontraumatic abdominal pain, especially if localized in the right lower quadrant (13). Later generation scanners give much more accurate images, and recent studies suggest that – for common problems such as appendicitis, diverticulitis, pancreatitis, and small bowel obstruction – intravenous contrast is no longer necessary.

Basak et al. studied 164 consecutive patients with less than 48 hours of nontraumatic abdominal pain who then underwent unenhanced abdominal CT scanning (14). Of these 164 patients, 71 had a definitive diagnosis made based on this scan. The other 93 patients then received intravenous contrast material and were rescanned. Experienced radiologists then interpreted both enhanced and unenhanced studies. In only one case did contrast permit both readers to make a positive diagnosis with contrast CT after a negative unenhanced scan, but the readers did not agree on the final diagnosis! At least two other studies have also shown no additional diagnostic accuracy by adding intravenous contrast to abdominal CT scans (15,16).

**Conclusion:** Intravenous contrast material does not improve the accuracy of noncontrast abdominal CT scans for most common problems. Again, your radiologist may feel more comfortable asking for this enhancement, and you should discuss your concerns at your local institution.

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#### **Question 5: What's the connection between seafood / shellfish allergy and intravenous contrast material, and how much should I worry about it?**

What's the connection?? None.

But this is one that won't go away, so we'll look at it a little more closely. Iodine is a ubiquitous and essential trace mineral; hence, it is not possible for someone to be "allergic to iodine." Ingested iodine is converted to iodide, the ionized form of iodine, in the gut. Dietary sources include fish, iodized salt, and iodates used as bread preservatives. Simple molecules such as iodine or contrast material do not have the complexity necessary for antigenicity (although they might act as haptens) (17).

Hypersensitivity to seafood can manifest as anything from itching and bronchospasm to vomiting and shock within two hours of exposure; these are true allergies related to immunoglobulin E (IgE). The responsible seafood antigen has been described as the fish equivalent of the muscle protein tropomyosin; there is no evidence that the iodine content of seafood has any relationship to these reactions (18).

Contrast materials contain a small amount of free iodine. Adverse reactions can be classified as either

idiosyncratic or nonidiosyncratic. The mechanism for the former is unknown and is termed "anaphylactoid", "allergy-like", or "pseudoallergic", rather than allergic. They are random and unpredictable events, although patients with a history of asthma or who take beta-blockers appear to be at increased risk. Pre-testing has no value, and a history of allergy to foods containing iodine is of no worth in predicting adverse reactions.

Nonidiosyncratic reactions are due to direct toxic or osmolar effects and are extraordinarily rare.

**Conclusion:** There is no literature to support seafood allergy as a specific, unique contraindication to the administration of intravenous contrast material. Most reactions are random and unpredictable.

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**Question 6: If someone says they're allergic to intravenous contrast, can't we just give them some diphenhydramine and steroids before they're injected?**

Every year more than 60,000,000 people are exposed to an iodinated contrast medium for the purposes of imaging (21). The incidence of serious allergy in these patients is small, although real. Shehadi showed in a very large cohort of 112,003 patients that the overall incidence of adverse reactions was 5.65%, of which 3.77% were mild, 1.77% were moderate, 0.02% (n=22) were severe, and 0.0007% (n=1) were fatal (22).

If a patient reports a prior history of reaction, shouldn't we expect another reaction with re-exposure to the contrast medium? Surprisingly, no – the incidence of re-occurrence runs between 8 and 25% (23). By asking the patient (in a non-leading question) to "Describe the reaction you had," you can restrict the use of a preparatory regimen to those in whom the reaction was moderate or severe. If it was minor, such as itching or hives, no prep is necessary.

The protective effect of H1 antihistamines and corticosteroids in high-risk patients has been demonstrated, but in non-randomized studies. By giving 50 mg of prednisone 13, 7 and 1 hour, and 50 mg diphenhydramine one hour prior to the administration of non-ionic contrast in 120 patients who had previous reactions to contrast, there was only one minor reaction (24).

Several other preparatory regimens have been described, but only a few have been carefully studied with randomized, double-blinded studies. Two meta-analyses published in 2006 found a handful of adequate studies for analysis: a few tested H1 antihistamines, a few tested corticosteroids, and one tested an H1-H2 combination. No study looked at an H1 antihistamine – corticosteroid combination (25,26). All authors agree that there is no advantage to giving preparatory medications to people who have no prior reactions to contrast material.

**Conclusion:** If the patient has a prior history of severe allergy or anaphylaxis, you should use a preparatory regimen, although the literature shows that it probably does not diminish the incidence of severe reactions. In addition, prophylaxis must be started 12 hours prior to the study – and definitely not less than 6 hours (27). This is obviously very impractical in the Emergency Department setting. Patients without prior reactions require no preparation.

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**Question 7: What about the patient with a history of asthma – does that really increase the risk of anaphylaxis?**

A history of multiple drug allergies or asthma is associated with a five-fold increased incidence of reactions to iodinated contrast materials; the rate for severe reactions increases from 0.02% to 0.1% (28). However, no unique precautions are necessary, and most reactions in such patients will be minor. There is no need to avoid a contrast exam. But make sure an asthmatic has a beta-agonist inhaler at hand.

**Conclusion:** A prior history of asthma or multiple allergies is no reason to withhold contrast material or begin a long prophylaxis protocol. Be aware there is a 1-in-a-1000 chance the patient will develop a severe reaction, which can be treated like any other anaphylactic reaction.

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**Question 8: Do we need a creatinine on everyone before performing contrast studies?**

Irrespective of cause, preexisting impairment of renal function is the most important risk factor for the development of contrast-induced nephropathy (CIN) (29). CIN is defined as an absolute increase in Serum Creatinine (SCr) of 0.5 mg/dL (44 µmol/L) or a relative increase of 25% within 48 hours of exposure to intravenous contrast. Although these changes sound trivial, they are associated with clinically important adverse short- and long-term outcomes (30,31). Whether increased morbidity and mortality is a direct result of the nephropathy or whether the nephropathy itself simply serves as a marker is unclear, but there's no denying this relationship: in-hospital development of acute renal failure from radiocontrast materials is associated with a 34% mortality rate (32).

If a patient has a baseline creatinine level of 2.0 mg/dL (176 µmol/L) or higher, the occurrence of CIN increases by 30 to 50% (33,34). Risk increases exponentially with increased serum creatinine concentration, varying from 2% in those with baseline creatinine of <1.5 mg/dL to 20% in those with levels of >2.5 mg/dL (35).

Diabetes mellitus accompanied by renal insufficiency is an independent risk factors for CIN. Some authors suggest that diabetes alone is an independent risk factor (36), but recent research has failed to corroborate this association (37). Other risk factors are shown in Table 1.

There have been several attempts to develop a risk stratification tool, but not one of these tools has been prospectively validated. All of these risk stratification tools were developed from data obtained from patients undergoing percutaneous coronary interventions, a different cohort from our patients in the Emergency Department (38,39). Nonetheless, the factors mentioned above seem to serve as independent risk factors for the development of CIN.

**Conclusion:** Do a careful history. If there is any question of prior renal insufficiency, check a serum creatinine level. If the patient is old, frail, septic, volume depleted, or has multiple myeloma or diabetes, it is prudent to check a creatinine, especially if the patient is taking ACE inhibitors, furosemide, or a nonsteroidal anti-inflammatory agent. The vast majority of patients do not need a serum creatinine and can safely receive a bolus of contrast material without fear of CIN.

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**Question 9: Can we prevent contrast-induced nephropathy (CIN) by prepping the patient with n-acetylcysteine, theophylline, mannitol, bicarbonate, or with another intervention?**

This is a very hot topic, with several summary articles having been published in the past year or so. Several risk factors for CIN – patient co-morbidities, ionic concentration of contrast material, volume of contrast material – are out of our hands. The best treatment is, of course, prevention and an alternative diagnostic study should be sought for anyone who is at high risk for CIN (see Table 1 for many known risk factors).

<b>Table 1: Risk Factors for Contrast-Induced Nephropathy</b>		
<b>Patient related</b>		<b>Not patient related</b>
Chronic kidney disease	Diabetes mellitus	High osmolar contrast
Urgent procedure	Multiple myeloma	Ionic contrast
Congestive heart failure	Advanced age (>70 years)	High contrast viscosity
Hypertension	Low hematocrit	High contrast volume
Hypotension	LVEF <40%	
Peripheral vascular disease	Atopic allergies	

There are apparently no randomized controlled trials evaluating hydration alone to prevent CIN, but this is a logical preventive therapy. The optimal hydration solution is unclear, but thought to be isotonic saline solution (40). Even better, apparently, is an isotonic sodium bicarbonate solution, made by removing 150 mL of dextrose 5% from a one-liter bag and replacing it with three ampoules of 8.4% sodium bicarbonate (41). By giving patients 3 mL/kg per hour for one hour prior to contrast, followed by 1 ml/kg per hour for six hours afterward, the rate of CIN was reduced from 13.6% in the saline group to 1.7% in the bicarbonate group. This method is safe, inexpensive, and can be easily accomplished in a busy Emergency Department. Although the bolus of 3 mL/kg may initially sound large, it is actually just 210 mL for a 70 kg patient – less fluid than an 8 ounce cup of coffee, which contains 240 mL.

Although the use of diuretics to "flush" contrast through the kidneys makes intuitive sense, studies have shown that forced diuresis with either mannitol or furosemide actually increases the occurrence of CIN (42). Simultaneous dialysis in high-risk patients might actually be cost-effective if it prevented the long-term complications of CIN; but studies have shown that even this aggressive approach does not work (43).

Several researchers have looked at increasing renal blood flow using vasodilators such as dopamine and fenoldopam. Again, this intuitively should prevent CIN. Results for both drugs are disappointing and neither method is recommended (44). Other vasodilators – atrial natriuretic peptide, calcium channel blockers, angiotensin-converting enzyme inhibitors, and endothelin receptor antagonists – have also shown disappointing results and cannot be recommended.

Aminophylline/theophylline has been analyzed in several studies, but results are conflicting. A few studies favor aminophylline/theophylline over placebo, but only one reached statistical significance (45).

Many studies have involved the antioxidant n-acetylcysteine (NAC). Its mechanism of action is unknown, but it is thought to scavenge oxygen free radicals or enhance the vasodilatory effects of nitric oxide. Hoffmann et al. suggest that NAC actually interferes with the proper measurement of serum creatinine and does nothing to prevent CIN (46). There are at least 22 trials using NAC (and 12 meta-analyses based on these 22 trials), but the available data are still unclear. Both oral and intravenous NAC have been studied, and there is just too much inconsistency in the results to state that this is a standard of care (47). Almost every NAC study requires a dose at least 6 hours prior to the procedure, which eliminates its use in the ED. One study bears promise: 80 patients with a mean baseline SCr of 1.8 mg/dL (160 µmol/L) received either 150 mg/kg intravenous NAC or isotonic saline about 30 minutes before cardiac catheterization. CIN occurred in 2/41 in the NAC groups and 8/39 in the saline group (48). Further studies are needed.

Finally, there's an intriguing study using ascorbic acid – Vitamin C (49). The authors conducted a randomized, double-blind, placebo-controlled trial of ascorbic acid in 231 patients with a serum creatinine concentration  $\geq$  1.2 mg/dL who underwent coronary angiography. They gave 3 grams of ascorbic acid at least 2 hours before the procedure and 2 grams in the night and the morning after the procedure and compared results to oral placebo. CIN occurred in 11 of the 118 patients (9%) in the ascorbic acid group and in 23 of the 113 patients (20%) in the placebo group. Vitamin C from the local health food store is dirt cheap – about a nickel for one gram. There's also virtually no downside. Should you change your practice based on one study? Well we've done it before for high-dose steroids and spinal cord injury (50) and fibrinolytics for ischemic stroke (51), and both of those therapies had potentially huge downsides.

**Conclusion:** There is no good data that allow us to prophylax Emergency Department patients against CIN. While NAC, sodium bicarbonate, and vitamin C all offer promise, the results are limited and further studies are required.

**Table 2: What You MIGHT Consider to Prevent CIN, Based on a Handful of Studies**

**1) If 0 or 1 CIN risks**

Before procedure	IV D5W + NaHCO <sub>3</sub> 3 amps at 3 mL / kg x 1 hour
During procedure	Low volume iso-osmolar contrast
After procedure	IV D5W + NaHCO <sub>3</sub> 3 amps at 1 mL / kg x 6 hours

**2) If 2 or more CIN risks, do #1 PLUS**

150 mg/kg intravenous NAC about 30 minutes before procedure and 600-1200 mg orally twice daily for 2 doses after procedure

**OR**

Ascorbic acid 3 g orally 2 hours before procedure and 3 g orally twice daily the day after procedure

**Question 10: What do I really need to know about the patient who takes metformin and needs a study requiring intravenous contrast?**

Although metformin is the most common medication used to treat type II diabetes, its exact mechanism of action is unknown. Metformin-associated lactic acidosis (MALA) has been reported in the literature more than 120 times, with a mortality of 50% (52). The manufacturers of metformin said in 1996 that metformin should be withheld 48 hours before and after the use of contrast material, due to an increased risk of lactic acidosis (53). Later this recommendation was amended to allow metformin before the exposure to contrast, but to withhold the medication for at least 48 hours afterward (54). But lactic acidosis after exposure to intravenous contrast occurs in diabetics who do not take metformin at a rate similar to those who do take it, and that occurrence is extremely low (55).

A comprehensive literature search, including data reported to drug manufacturers, unpublished data, and reports to the FDA, turned up a total of 18 cases of MALA in patients who received intravenous contrast material (56). Sixteen (and probably 17) of these 18 patients took metformin despite a contraindication to doing so (see Table 3).

Thus, in the entire world literature there is exactly one case report of a patient appropriately prescribed metformin who developed renal failure after intravenous contrast.

**Table 3: Contraindications to taking metformin**

- Hypersensitivity to metformin
- Diabetic coma and ketoacidosis
- Impaired renal function (even mild)
- Chronic liver disease
- Cardiac failure
- Recent myocardial infarction
- Shock or severe systemic disease
- Pulmonary insufficiency
- Vitamin B12 deficiency

**Conclusion:** If your patient takes metformin and needs a contrast study, check the creatinine. If it is normal, proceed as you would if the patient were not taking metformin. There is no increased risk of lactic acidosis.

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I hope this essay has helped you with some current evidence about questions we frequently encounter when deciding whether a patient in the Emergency Department should have an abdominal CT scan. Some of the evidence is pretty sound, while other evidence is still shaky.

As always, I welcome your comments at [joe@joelex.net](mailto:joe@joelex.net).

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