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Anaphylactoid Reactions after Instillation of Contrast Material into the Urinary Tract: A Survey of Contemporary Practice Patterns and Review of the Literature

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Abstract:

Objectives: To assess drug reactions (ADRs) encountered by practicing urologists for contrast instilled into the urinary collecting system, and to describe current practice patterns regarding contrast administration into the urinary tract for patients with known contrast allergies.

Methods: Endourological Society members were e-mailed a web-based survey about their prior experience with contrast-related ADRs and practices for contrast administration into the urinary tract among patients with known intravenous contrast allergies. Chi-squared analysis was used to compare management patterns between patients with established allergies and those without.

Results: An estimated 2300-2500 e-mails were reached, resulting in an estimated response rate of 6.3-8%. Over 75% of respondents were fellowship trained. Average time in practice was 16 years, and respondents performed a mean of 6.7 urologic contrast studies per week. 6.7. 32.6%,

14.7%, and 4.0% had treated at least 1 patient with a mild, moderate, or severe reaction, respectively. Contrast-related ADRs were most commonly associated with retrograde pyelogram (50%). For patients with known contrast allergies, 5.4% pursue additional work-up before administering contrast in the urinary tract. Pre-treatment with antihistamine or steroids is used by 24.8% and 23.4%, respectively. When performing retrograde pyelograms for such patients, urologists are more likely to use dilute contrast ($p=0.003$), but otherwise do not significantly alter technique.

Conclusions: Contrast ADRs are encountered not infrequently among practicing urologists. There is notable practice variation in the management of patients with known contrast allergies, though the overall perceived risk of contrast use in these patients is low, provided good technique is used.

Introduction:

While adverse drug reactions (ADRs) to iodinated contrast material are well documented in the literature, most of these relate to the intravascular administration of contrast, where the reported incidence is 1-12%.^{1,2} The range of reactions is broad, from urticaria to anaphylactoid; however, most are mild. The use of non-ionic low osmolar iodinated contrast agents has further reduced the frequency of such events, with a reported rate of 0.2-0.6%.³

In contrast, ADRs from contrast material instilled within the urinary collecting system during fluoroscopic imaging studies are rare, with most of the literature comprised of isolated case reports. Historically, the rate of contrast-related allergic reactions was 0.26% following voiding cystourethrogram (VCUG) or retrograde pyelogram (RPG).⁴ More contemporary research by Blackwell and colleagues using administrative hospital discharge data revealed an overall rate of 0.48% among patients undergoing RPG, antegrade nephrostogram, cystogram, or loopogram, with 87% of these being mild reactions.⁵ Yet, this study was unable to evaluate more specific aspects of care or specific provider-level practices for patients receiving such studies.

The specific practice patterns of urologists performing RPG, VCUG, and nephrostogram remains poorly defined, particularly for patients with known intravenous (IV) contrast allergies. Moreover, there are no suggested guidelines from the American College of Radiology or American Urological Association on this issue, likely secondary to the paucity of evidence. In this study, we assess contrast-related ADRs among the endourology community, and describe practice patterns and trends for contrast utilization in fluoroscopic imaging studies among this group. Specifically, we determine whether there are any differences in management patterns between patients with known allergies to IV contrast and those without.

Materials and Methods:

The Endourological Society is an international group of endourologists with a goal of facilitating scientific dialogue and training among its members, and it was chosen for this study due to the high volume of endoscopic cases likely to be performed by its members. We constructed a 15-question survey containing questions regarding respondents' demographics, educational background, and experience with ADRs secondary to contrast material in the urinary collecting system. Investigators first sought input from various providers who identified that the topic was important. After reviewing the literature, a focused group discussed relevant aspects and identified gaps in knowledge in regards to practice patterns. Items were created and piloted to a small group of urologists for further feedback prior to dissemination. The questionnaire format was a combination of multiple-choice, drop-down menus, and short answer write-in (Appendix 1). This was hosted by a web-based survey host, "surverymonkey.com."

The survey was submitted for approval to and then distributed by the Endourological Society to its members electronically via e-mail. At the time of survey administration, there

were an estimated 2300 to 2500 functional e-mails on the Endourological Society mailing list; it was not possible to determine the exact number of actual recipients who received the e-mail and opened the survey link. A reminder email was distributed 1 month following the initial contact. Respondents were asked to enter the first letter of their last name and year of birth to create a unique identifier, which was used to screen for duplicate submissions. IRB approval was not required for this survey study.

Survey responses were screened for duplicate submissions and non-responses to specific questions. For each question, all write-in options were reviewed for additional relevant responses that were not captured by the original answer options, and these were included for analysis. As not all respondents answered all questions on the survey, each question was analyzed separately and the relevant response rate for a given question was determined relative to the number of total responses for that specific question. For questions pertaining to reported cases of contrast-related ADR, responses were deemed inaccurate and excluded from analysis if the number of plausible responses exceeded the reported number of cases. Chi square analysis was used to determine significant differences in management patterns between patients without a known contrast allergy and those with established allergy to IV contrast agents.

Results:

Over a 6-week period, 185 responses were collected. Based on the estimated number of active e-mails reached, the overall response rate is estimated to be between 6.3 and 8%. Participant demographics are included in Table 1. Fifty-seven percent of respondents practiced within the United States or Canada and all American Urological Association sections were represented. Over 75% of respondents were fellowship trained, with the majority in endourology.

On average, respondents had completed training a mean of 16 years prior to survey completion (standard deviation 9.5, range 1-38). An average of 6.7 urologic contrast studies was performed each week (standard deviation 5.6, range 1-30).

A total of 93 cases of ADR to contrast instillation following RPG, VCUG, or nephrostogram were reported by 184 individuals (50.5%); one respondent additionally reported a case of contrast-induced nephropathy requiring dialysis. Another declined to respond and was therefore excluded from further analysis. Among the remaining urologists (n=184), 32.6%, 14.7%, and 4.0% had treated at least 1 patient whose reactions were mild, moderate, or severe, respectively (Figure 1). Among reported symptoms, urticaria was most common (53.0%). Dyspnea and wheezing comprised 11.4% of reported symptoms, and hypotension 9.6%. There was 1 case of cardiac arrhythmia, but no reported sequelae of cardiopulmonary arrest or death. Symptoms resolved without intervention in 67 cases.

ADRs were most commonly associated with RPG (50%), followed by nephrostogram (12.7%). VCUG comprised 6.4% of contrast-related ADRs. Among respondents who could recall the specific contrast medium used (n=68), non-ionic contrast was utilized in 82.4% of cases, half of which involved iohexol (OmnipaqueTM).

In current practice, 8.3% of survey respondents (n=151) would not administer contrast within the urinary tract for patients with a known IV contrast allergy. Prior to proceeding with a urologic study such as RPG, VCUG, retrograde urethrogram (RUG), or nephrostogram, 5.4% (out of n=146) would choose to perform additional medical work-up such as skin-testing for these patients. Among these, 24.8% and 23.4% would administer an antihistamine or steroid as pre-treatment, respectively. This was significantly higher than the rates of antihistamine or

steroid pre-treatment for patients without identified contrast allergies (1.2% and 2% respectively, $p<0.0001$).

With regard to management practices around RPG, 15% of urologists ($n=150$) reported no particular precautions or techniques that were practiced for patients with known allergies to IV contrast. There was no difference reported in the size of the syringe used to instill contrast ($p=0.25$), type of contrast ($p=0.99$), or volume of instilled contrast ($p=0.07$). However, there was a significant difference regarding the degree of contrast dilution between patients with known contrast allergies and those without (Figure 2), with more dilute contrast used among the latter ($p=0.003$).

Among those who elaborated on their specific management practices ($n=52$), 32.7% reported attention to avoiding overdistension of the collecting system by excessive volume or pressure. Three individuals reported sincere consideration of avoiding endoscopic contrast use altogether and preferential use of air during percutaneous nephrolithotomy in these patients. Additionally, two urologists specifically remarked upon the importance of maintaining urothelial integrity with atraumatic technique.

Comments:

In this survey study among endourological society members, a high proportion of individuals have witnessed contrast-related allergic reactions following instillation of contrast during VCUG, RPG, or nephrostogram. Nearly a third of surveyed individuals had encountered at least a mild reaction in the course of his or her careers. Notably, in our study, approximately 25% administer medical prophylaxis to those with IV contrast allergies prior to instilling contrast in the collecting system, and over 8% defer the utilization of contrast altogether. Few perform

further medical work-up, such skin testing, for these patients prior to proceeding with administration of contrast in the urinary tract. We also find that providers are more likely to dilute contrast for patients with known contrast allergies when performing RPG.

Such contrast-related allergic reactions are thought to be due to absorption of contrast across the urothelium, with a wide variety of clinical symptoms resulting from IgE-mediated release of histamine, complement, and kinin.^{3,4,6-8} Risk factors include highly concentrated contrast media, contrast administration under pressure, large contrast volumes, and delayed drainage.^{4,9,10} These principles are generally accepted by urologists, with many respondents within this survey specifically mentioning particular care to avoid over-distension of the collecting system. Given that pyelovenous backflow has been reported in as many as 18% of RPG cases, appropriate technique is critical for safe RPG in patients with known contrast allergies.¹¹

Current strategies to minimize the risk of contrast ADRs for patients undergoing IV contrast exposure include pre-medication with prednisone or methylprednisone several hours prior to contrast administration, with consideration for diphenhydramine 1 hour prior.³ Among high risk patients with identified contrast allergies, such regimens have been shown to result in low rates of allergic reactions.¹² However, breakthrough reactions still occur in about 2.1% of individuals, and the type or severity of reaction does not appear to be mitigated by prophylaxis.¹³ Though it has been suggested that this strategy also be considered for high risk patients undergoing instillation of contrast into the urinary tract, the role and current use of pre-medication in this setting remains unknown.^{4,5}

We find that nearly a quarter of surveyed urologists would administer prophylaxis with a steroid or anti-histamine for patients with known contrast allergies before performing any

urologic imaging study requiring contrast instillation in the collecting system. Notably, among surveyed members of the European Society of Urogenital Radiology, few would give prophylactic medications in such high risk patients before cystography (8%), though a similar percentage would prior to RPG (22%).¹⁴ This may be due to a greater theoretical risk of pyelovenous backflow during RPG, which has been cited by others as a consideration.⁵ The high rate of pre-medication seen in this study may follow a similar rationale as that for pre-medication prior to IV contrast studies, with low perceived risk and high potential benefit to pre-treatment for high risk patients with known contrast allergies.¹⁵

Additional practices to minimize risk of IV contrast agents mentioned by respondents include skin testing to determine which alternative contrast agents may be safely tolerated. Among patients with known IV contrast allergies, the negative predictive value of this test is as high as 93.1%.¹⁶ The utility of contrast dilution, which was also mentioned by several survey respondents, remains unproven; beyond a threshold level, anaphylactoid reactions to IV contrast media do not appear to be dose-dependent.¹⁷ Thus, the efficacy of this practice to prevent contrast ADR from RPG remains unknown.

The current literature on ADR from contrast instilled into the urinary tract remains scant and is mostly limited to case reports (Table 2). While contrast ADRs have been most commonly reported after VCUG and RPG, they have also been noted to occur following RUG and loopogram studies, suggesting that there may be a reasonable risk of anaphylactoid reactions to contrast administered for these urologic studies as well.^{18,19} In light of recent research affirming the low historic rates of ADRs following administration of contrast in the urinary tract, future work is warranted to better assess the utility of pre-medication regimens in this context and further elucidate the motivations behind differing practice patterns surrounding this rare event.

Our study is not without limitations. As this survey was sent only to a subset of practicing urologists, the responses are not representative of the general population of practicing urologists in the United States or internationally. Though nearly a quarter of respondents were not fellowship-trained, nearly two-thirds were fellowship trained in endourology, which may have biased the responses. There is also recall bias inherent in the survey questionnaire format, which may further influence these results. However, we believe that a contrast-related ADR is a memorable event in the course of one's clinical practice, particularly if severe, and would likely be recalled with reasonable accuracy by most urologists. While high non-response rates may potentially bias the results of the study, similar descriptive surveys in the radiologic literature with comparable response rates have been deemed acceptable and remain informative.²⁰

Due to unanswered questions, we were unable to completely capture the total number of fluoroscopic imaging studies performed by all of the survey respondents, and were therefore unable to calculate overall rates of contrast ADR. However, based on the average number of years out of practice and average number of weekly fluoroscopic studies reported by respondents, we estimate that about 3310 cases overall are represented by this survey. This would result in an estimated contrast ADR rate of about 2.8%, which remains higher than rates reported in the literature.^{4,5} Thus, this remains a pertinent and relevant topic for those in clinical practice.

Conclusions:

Despite low published rates of contrast-related ADR in the literature, this survey reveals that many urologists have treated a patient with an allergic reaction to contrast instilled into the urinary collecting system during the course of his or her career. Though nearly a quarter of

urologists would pre-treat with steroids or antihistamines, there are few other specific practices that are performed for patients with known ADRs to IV contrast if good technique is used, suggesting that the overall perceived risk of such studies among these patients is low. There remains limited data regarding the use of contrast in the urinary tract among patients with known IV contrast allergies, and further work is warranted to better define what informs these practice patterns.

Appendix 1: Survey questions administered to Endourological Society members

1. In which AUA section do you primarily practice?
 - a. Mid Atlantic
 - b. North Central
 - c. Northeastern
 - d. New England
 - e. New York
 - f. South Central
 - g. Southeastern
 - h. Western
 - i. If outside of the United States, please list country: _____
2. In what year did you complete residency (i.e., 1994)? _____
3. Did you complete fellowship training? If so, in what?
 - a. No fellowship completed
 - b. Andrology
 - c. Endourology +/- minimally invasive surgery
 - d. Female
 - e. Infertility
 - f. Oncology
 - g. Pediatrics
 - h. Transplant
 - i. Trauma and Reconstruction
 - j. Other (please specify) _____
4. On average throughout your career, how many endoscopic contrast studies (i.e., retrograde pyelograms, retrograde urethrograms, voiding cystourethrograms, nephrostograms, etc) have you performed per week? _____
5. How many patients have you treated who experienced an adverse reaction to contrast placed ENDOSCOPICALLY within the urinary tract?

- a. Mild (e.g., Urticaria) _____
- b. Moderate (e.g., Dyspnea/Wheezing, Hypotension) _____
- c. Severe (e.g. Arrhythmia, Cardiopulmonary arrest, Death) _____
- d. Other (please specify) _____

The following questions ask you to recount prior adverse reactions to contrast in the urinary system. If you have encountered more than 5 patients, please enter data for all severe reactions. Please add comments.

6. Of patients you have encountered with adverse reactions to contrast in the urinary system, what were their symptoms?

	I do not recall	Hypotension	Cardiac arrhythmia	Cardiac arrest	Pulmonary arrest	Urticaria	Dyspnea	Wheezing	Other
Prior Patient 1	☐	☐	☐	☐	☐	☐	☐	☐	☐
Prior Patient 2	☐	☐	☐	☐	☐	☐	☐	☐	☐
Prior Patient 3	☐	☐	☐	☐	☐	☐	☐	☐	☐

Other (please specify)

7. For the patients mentioned above (e.g., Patient 1, Patient 2, Patient 3), what was the gender, approximate age, imaging study, and type of contrast used?

	Gender	Aprox. Age	Exam	Type of contrast
Prior Patient 1				
Prior Patient 2				
Prior Patient 3				

If other (please specify)

Gender:

- ☐ Male ☐ Female

Approximate age:

- ☐ I do not recall ☐ <18 ☐ 19-30 ☐ 31-65 ☐ >66

Exam type:

- ☐ I do not recall ☐ nephrostogram ☐ retrograde pyelogram
☐ retrograde urethrogram ☐ voiding cystourethrogram ☐ other

Type of contrast used:

- ☐ I do not recall ☐ iodixanol (Visipaque) ☐ iohexol (Omnipaque)

- ☐ ipamidol (Isovue) ☐ itrolan (Isovist) ☐ ioversol (Optiray)
☐ meglumine ioxaglate (Hexabrix) ☐ sodium oxalate ☐ other

8. Do you recall any interventions for these patients (e.g., Patient 1, Patient 2, Patient 3)?

	I do not recall	None, spont. resolution	Antihistamine	Steroids	Intubation	CPR	ICU admit	Other
Prior Patient 1	☐	☐	☐	☐	☐	☐	☐	☐
Prior Patient 2	☐	☐	☐	☐	☐	☐	☐	☐
Prior Patient 3	☐	☐	☐	☐	☐	☐	☐	☐

If other (please specify)

9. Did any of these patients above (e.g., Patient 1, Patient 2, Patient 3) have a known prior allergy to IV contrast?

	I do not recall	Yes	No
Prior Patient 1	☐	☐	☐
Prior Patient 2	☐	☐	☐
Prior Patient 3	☐	☐	☐

10. In patients with known IV contrast allergies, do you inject contrast within the urinary system during endoscopic procedures (retrograde pyelogram/urethrogram, voiding cystourethrograms, nephrostograms, etc)?

- Yes
- No (if No skip to next question)
- Other (please specify)

11. In patients with known IV contrast allergies, do you routinely perform any additional medical workup prior to endoscopic contrast injection (e.g., skin testing)?

- Yes (briefly explain) _____
- No
- Additional work-up

12. Do you routinely administer antihistamines and/or steroids prior to endoscopic injection of contrast?

	No	Steroids	Antihistamine
No Known Drug Allergies	☐	☐	☐
Contrast Allergy	☐	☐	☐
Other (please specify)			

13. How do you typically administer contrast during a retrograde pyelogram in each of the following patients:

	Syringe Size	Average Contrast Volume	Contrast	Dilution
No Known Drug Allergies				
Contrast Allergy				
Other (please specify)				

Syringe Size:

☐ 5 cc ☐ 10 cc ☐ 30 cc ☐ 60 cc ☐ Other

Average Contrast Volume:

☐ <10 cc ☐ 10 cc ☐ 20 cc ☐ 30 cc
☐ 40 cc ☐ 50 cc ☐ 60 cc ☐ 70 cc
☐ 80 cc ☐ 90 cc ☐ 100 cc

Contrast:

☐ I do not recall ☐ iodixanol (Visipaque) ☐ iohexol (Omnipaque)
☐ ipamidol (Isovue) ☐ itrolan (Isovist) ☐ ioversol (Optiray)
☐ meglumine ioxaglate (Hexabrix) ☐ sodium oxalate ☐ other

Dilution:

☐ unknown ☐ full strength ☐ diluted to 1/2 strength
☐ diluted to 1/4 strength ☐ diluted to 1/8 strength ☐ other

14. Please provide any additional comments you feel are important

15. Please enter an email below to participate in an optional raffle for a \$50 Amazon.com gift card. Your e-mail will only be used to send the gift card.

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Figure Legends:

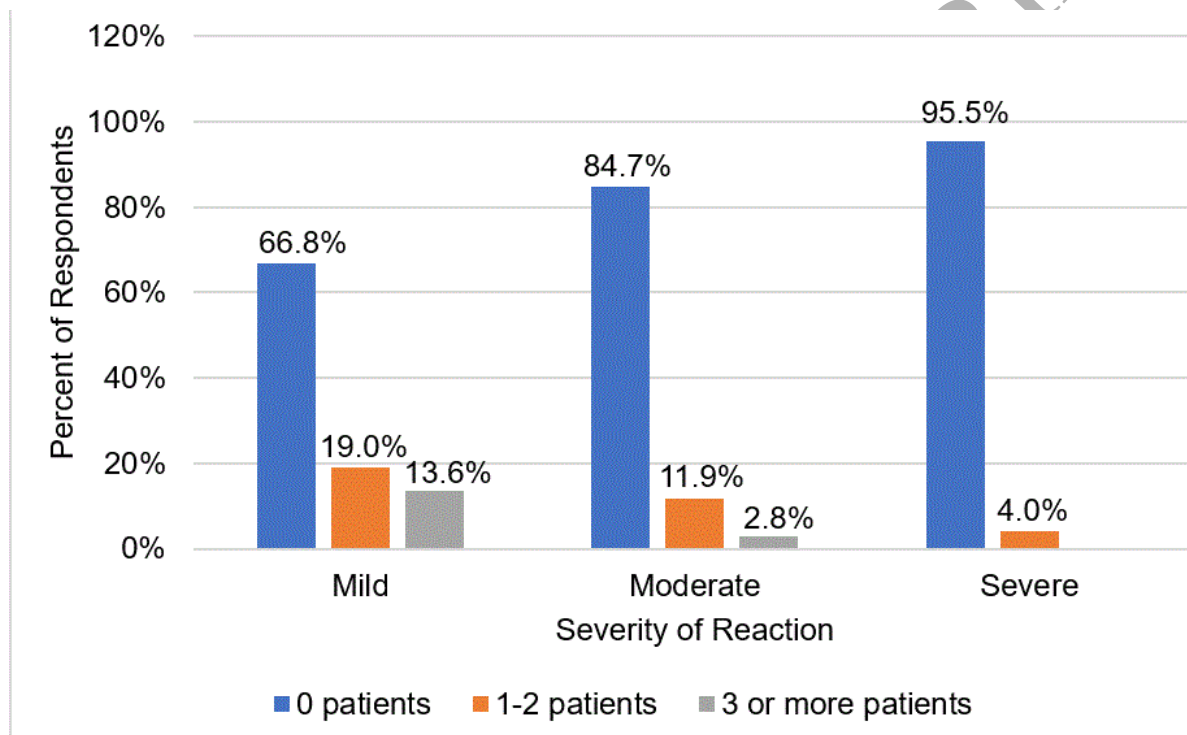


Figure 1: Reported clinical experience with adverse reaction to extravascular contrast used in the urinary collecting system, among survey respondents (n=184).

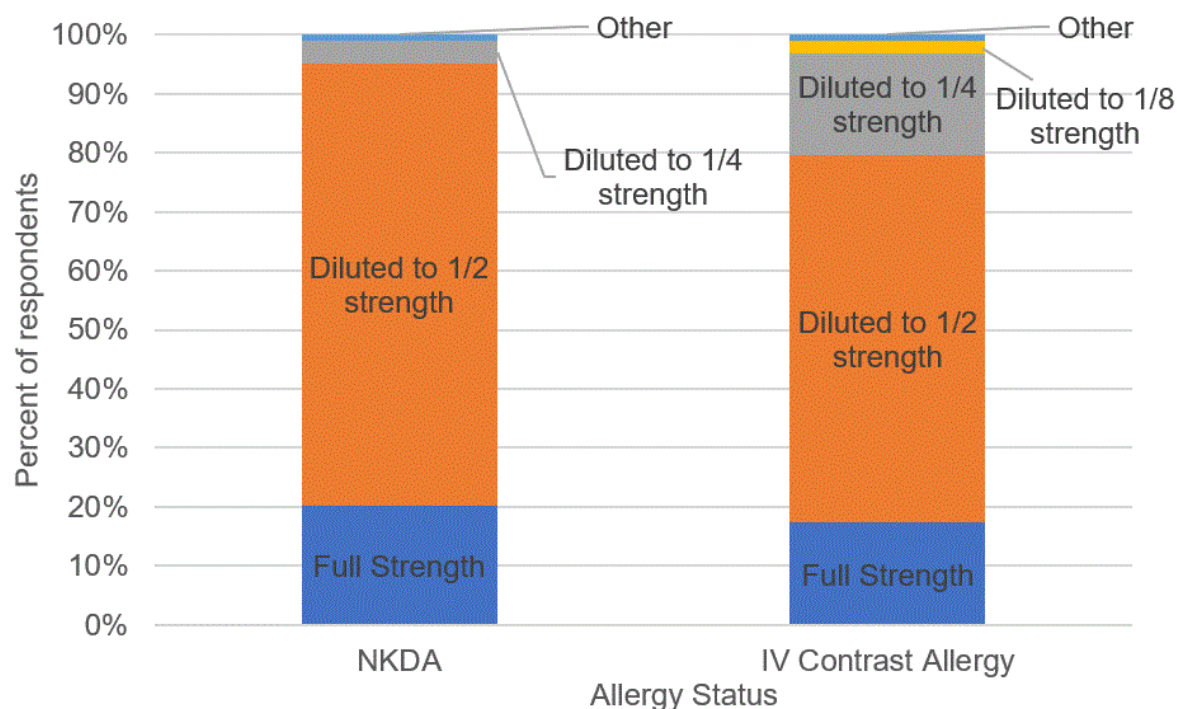


Figure 2: Differences in concentration of contrast used during retrograde pyelogram performed for patients with and without known adverse reactions to intravenous contrast (n=147). NKDA = no known drug allergies; IV = intravenous.

Table 1: Demographics and professional characteristics of survey respondents from the Endourological Society e-mail list. AUA = American Urological Association.

Characteristics	Number of Respondents (% of total)
Geographic Location	
AUA Sections (United States/Canada)	105 (56.8%)
Mid-Atlantic AUA Section	5 (2.7%)
North Central AUA Section	13 (7.0%)
Northeastern AUA Section	15 (8.1%)
New England AUA Section	4 (2.2%)
New York AUA Section	9 (4.9%)
South Central AUA Section	13 (7.0%)
Southeastern AUA Section	23 (12.4%)
Western AUA Section	13 (7.0%)
International	80 (43.2%)
Year of Residency Completion	

2010-present	14 (7.6%)
2000-2009	80 (43.2%)
1990-1999	46 (24.9%)
1980-1989	35 (18.9%)
1970-1979	7 (3.8%)
Question unanswered	3 (1.6%)
Fellowship training	
None	42 (22.7%)
Andrology	1 (0.54%)
Endourology/Minimally Invasive	118 (63.8%)
Oncology	14 (7.57%)
Pediatrics	1 (0.54%)
Other	5 (2.7%)
Average number of endoscopic contrast studies per week	
1-5	104 (56.8%)
6-10	51 (27.6%)
16-20	2 (1.1%)
>20	6 (3.2%)
Question unanswered	12 (6.5%)

Table 2: Current reported cases of contrast-related adverse drug events following instillation of contrast material into the urinary tract for fluoroscopic studies. RPG, retrograde pyelogram; VCUG, voiding cystourethrogram; RUG, retrograde urethrogram.

Series	Year	# of Cases	Exam Type	Type of Contrast	Pre-medication	Complications	Mortality
Schmidlapp ²¹	1961	1	RPG	30% sodium methylglucamine diatrizoates (Retrografin) + 50-70 mg neomycin	N/A	Respiratory and cardiac arrest	0
McAlister et. al ⁹	1974	1	VCUG	50% sodium ditrizoate; 5% sodium acetrizoate (Cystocon)*	N/A	Urticaria	0
Redman et. al ²²	1977	1	VCUG	50% sodium diatrizoate	N/A	Urticaria	0
Johanning ²³	1980	2	RPG	20% methiodal (Skiodan) + 0.5% neomycin	N/A	Shortness of breath, wheezing	0

			RPG	43% meglumine iothalamate (Cysto-CONRAY)	N/A	Dyspnea, wheezing, hypotension, ventricular fibrillation	0
Gupta, et al ¹⁸	1991	1	RUG	Not specified	N/A	"allergic reactions" (not specified)	0
Weese et. al ⁴	1993	2	VCUG	Iothalamate meglumine (Cysto-Conray II)	N/A	Urticaria	0
			VCUG	Iothalamate meglumine (Cysto-Conray II)	N/A	Hypotension, tachycardia, syncope	0
Armstrong et. al ²⁴	2005	1	RPG	50% iohexol (Omnipaque)/50% normal saline	50 mg prednisone at hour 13, 7, and 1 hour before surgery + 50 mg diphenhydramine 1 hour before surgery	Urticaria, dyspnea, wheezing, respiratory arrest	0
Pooli et. al ²⁵	2017	1	RPG	Not specified	10 mg dexamethasone + 50 mg IV diphenhydramine "prior to procedure"	Tongue swelling, facial and neck edema, difficulty breathing	0

*Same patient with urticarial reaction to two separate exposures

RPG, retrograde pyelogram; VCUG, voiding cystourethrogram; RUG, retrograde urethrogram