

MEDICAL IMAGING—REVIEW ARTICLE OPEN ACCESS

Adverse Reactions to Urinary Contrast: A Case Report and Systematic Review

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ABSTRACT

Objective: Intra-urinary iodinated contrast agents are commonly used in urological procedures, but research of allergic reactions is rare. This study presents a rare case of an intra-urinary contrast reaction, followed by a comprehensive literature review of adverse reactions to intra-urinary contrast.

Methods: PubMed and Embase databases were searched using Medical Subject Headings terms related to urinary procedures and contrast reactions, with additional articles identified through reference reviews.

Results: Adverse reactions to intra-urinary contrast agents are rare, with most reactions being mild. Severe reactions were infrequent, and both patient-related and contrast-related factors were identified as influencing the likelihood of adverse events. However, the role of previous intravenous contrast reactions as a predisposing factor and the effectiveness of premedication in preventing these reactions remain uncertain. Furthermore, clinical guidelines for diagnosing and managing such reactions are lacking.

Conclusion: Although urinary contrast reactions are uncommon, they can range from mild to severe, including anaphylaxis. Further research is needed to establish standardized premedication protocols and management strategies, and a better understanding of predisposing factors could enhance patient safety in urological procedures involving contrast agents.

1 | Introduction

Iodinated contrast (IC) agents are widely used in various diagnostic imaging procedures to enhance image clarity. However, they can sometimes trigger adverse reactions (ARs). The incidence of ARs associated with intravenous (IV) IC, the most common administration route, has been reported to range from

1% to 12% [1, 2]. In comparison, intra-urinary administration is considered to have a lower risk profile for ARs.

This article reports a notable case of an intra-urinary IC AR that occurred following nephrostomy and stent insertion in a patient with a known history of IV IC ARs. During the management of this case, we encountered limited data and guidelines on

Abbreviations: APG, antegrade pyelogram; ARs, adverse reactions; B/L, bilateral; CAD, coronary artery disease; CG, cystogram; CHF, congestive heart failure; CS, cystoscopy; CUG, cystourethrogram; HTN, hypertension; IC, iodinated contrast; ICU, intensive care unit; IV, intravenous; MeSH, medical subject headings; PCN, percutaneous nephrostomy; PCNG, percutaneous rephrostogram; PCNL, percutaneous nephrolithotomy; RA, retrograde access (RPG, Stent, ureteroscopy); RPG, retrograde pyelogram; RR, reaction rate; TURBT, trans urethral resection of bladder tumour; URG, urethrogram; URS, ureteroscopy; VCUG, voiding cystourethrogram; VUR, Vesicoureteral reflux.

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intra-urinary contrast reactions. To address this gap, we conducted a systematic review to compile comprehensive information on intra-urinary contrast allergies.

This review spans articles from 1989 to 2024, covering a wide array of urological procedures. It explores the incidence of ARs, identifies potential predisposing factors, and summarises the clinical manifestations of intra-urinary IC ARs. Additionally, it provides an overview of preventive measures and management strategies based on the current evidence.

2 | Case Report

A 57-year-old male with metastatic prostate cancer (Gleason score 5+5=10) involving the rectum and bladder presented with bilateral ureteric obstruction, hydronephrosis, and postrenal acute kidney failure.

The patient was referred to radiology for bilateral nephrostomy and stent placement. Due to a known history of allergic reactions to IV IC (specific type unknown), presenting as hives, he was premedicated with 50 mg of prednisolone and 10 mg of loratadine, which were administered orally 13h and 1h prior to the procedure, respectively. This procedure was performed with no ARs noted.

Four days later, the right nephrostomy became obstructed, requiring replacement, which procedure was planned in conjunction with the scheduled insertion of bilateral stents. No premedication was administered for this procedure, and immediately following the procedure, the patient experienced right eye pain, swelling, itching, and photophobia.

A retrospective review of the procedure record revealed that both procedures used Omnipaque 350 (iohexol 350) as per department protocol, although details regarding volume, concentration, and pressure were not documented.

Physical examination at the time showed swelling extending to the right cheek and temporal area. However, the patient's breathing remained clear and vital signs were within normal limits. He received 120 mg of oral fexofenadine and was monitored in the radiology department for 1h before being transferred back to the ward.

The urology team assessed the patient at ward 2h post-procedure and noted ongoing right eye swelling with stable vital signs; 10 mg of Loratadine was administered. The patient was re-assessed 7h post-procedure with no further complaints of eye symptoms.

3 | Systematic Review

3.1 | **Method**

A systematic review was conducted, and cases are described based on clinical details reported in these studies. Figure 1 shows the flow chart and process of the review.

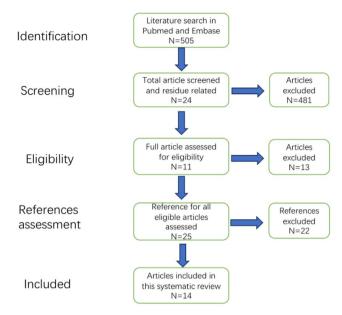


FIGURE 1 | PRISMA flow chart.

3.2 | Literature Search

The PubMed and Embase databases were searched for relevant literature. The search strategy employed Medical Subject Headings (MeSH) terms, including 'urology', 'urinary', 'urological', 'endourologic procedure*', 'retrograde pyelogra*', 'ureteroscopy', 'cystourography', 'contrast allergies,' and 'contrast adverse reactions' as well as synonyms for each term. Three researchers conducted the literature search independently to ensure comprehensiveness and minimise bias. Additionally, all references from the identified articles were reviewed, leading to the discovery of two additional related case reports.

3.3 | Article Selection

Articles were selected based on meeting all of the following inclusion criteria: (1) original research articles or case reports; (2) studies involving human subjects; (3) studies exploring the connection between urinary contrast media usage and adverse reactions; and (4) studies published since 1989. Any disagreements in study selection were resolved through discussion among the researchers to reach a consensus.

3.4 | Data Extraction

Key information was extracted from each included article, including the year and author of publication, study type, use of pre-medication, clinical characteristics of cases, types of contrast media used, specific urological procedures performed, predisposing factors for adverse reactions, number of participants, and management strategies employed.

4 | Results

A total of 14 articles were identified for this review, including five case reports, two web-based surveys conducted by the

	Author, Country, Year	Study type	Reaction	Number of participants and reaction rate	Procedures	Premeds	Contrast type	Possible predisposing factor	Management
1	Blackwell et al. [4] USA 2016	A cross-sectional respective review	Anaphylaxis, shock, angioedema, respiratory distress 13% (51/393) urticaria or iatrogenic hypotension 87% (342/393)	76.174 patients, $RR = 0.48\%$ $(n = 393)$	RPG, APG, CG	No data	ICb	old ^a , comorbidities, suspicious of urine infection, haematuria, VUR, Bladder cancer, previous IV contrast allergy	No data
7	Dai et al. [3] USA 2018	Web-based survey	53.0% of respondents saw urticaria 11.4% saw Dyspnoea and wheezing. 9.6% saw hypotension 1 case of cardiac arrhythmia.	184 (responding urologist)	RPG, VCUG, PCNG	50% respondents give antihistamine or steroid to patients with known history of IV contrast reaction.	Non-ionic contrast was utilised in 82.4% of cases, half of which involved iohexol (OmnipaqueTM).	Contrast volume and concentration, pressure in kidney, delayed contrast drainage, urothelial trauma	Self-resolved
ю	Moses et al. [13] USA 2018	A cross-sectional respective review	Urticaria, respiratory distress, tachycardia, hypotension, Anaphylaxis	2650 patients $RR = 4.2\%$ $(n = 113)$	PCNL and RA	31% $(n = 35)$ received either antihistamine or steroid	IC	Contrast osmolarity and volume, pressure in kidney * previous IV contrast allergy	No data
4	Mohapatra et al. [16] USA 2019	Web-based survey	No data	325 (responding urologist)	PCNL and URS	49% respondents give prophylaxis	IC	Contrast volume, bleeding occur, high pressure injection	No data
5	Weese et al. [5] USA 1993	Case report + retrospective review	n=1 urticaria/ $n=1$ anaphylaxis	783 patients in review, RR = 0.26% (n = 2)	VCUG and RGP	No data	Cysto-Conray (Iothalamate meglumine)	Contrast concentration and volume, pressure in kidney	Self-resolved $(n=1)$ Trendelenburg position only $(n=1)$

(Continues)

epinephrine, albuterol, methylprednisolone, Diphenhydramine, re-intubation and IV Fluid, Esmolol, 02, epinephrine, Management ICU admission hydrocortisone Intubation and ICU admission cietidine, No data No data No data previous IV reaction Known IV reaction disruption during Urothelial trauma epithelium injury reflux or bladder (n-1), Nil known contrast reaction TURBT, known reaction (n=2)contrast allergy predisposing Urinary tract history of IV Previous IV Haematuria, Urothelial Possible factor iohexol/50% normal 92.5 mg L/mL with radiocontrast dye Iodinated contrast Contrast type 2.5 mL of a 50% saline solution, Not mentioned 370 diluted to normal saline 140 mg L/mL, or Urografinlow pressure Omnipaque Urographin Nonionic or conray intravenously prior Diphenhydramine Steroid at 13/7/1h diphenhydramine Dexamethasone prior procedure and 50 mg of Benadryl 1h to procedure **Premeds** 10 mg and No data 50 mg 50 mg No data No data Videourodynamic RPG + bladder Procedures (luoroscope) contrast+ CS+B/L(bladder biopsy URG PCN RPG CG 11,714 patients, reaction patient participants RR = 0, (n = 0)and reaction Number of 5 patients, (n = 1)rate n=1 hypotension Anaphylactoid Anaphylactoid n=2 urticaria Anaphylactic Anaphylaxis symptoms Reaction reaction reaction reaction No data Letter to editor Letter to editor Letter to editor Study type Case report Case report Case report TABLE 1 | (Continued) Miller et al. [8] Gupta et al. [7] 11 Pooli et al. [10] Country, Armstrong Cartwright Author, et al. [6] et al. [9] et al. [12] Gaiser Year 2005 India 1993 2008 USA USA 1995 USA 1991 2017 $\overline{\text{UK}}$ 10 _ 9 ∞ 6

TABLE 1 | (Continued)

Author, Country, Year	Study type	Reaction symptoms	Number of participants and reaction rate	Procedures	Premeds	Contrast type	Possible predisposing factor	Management
Bettenay et al. [11] Australia 1989	Case report	Anaphylaxis	1	VCUG	No data	65% angiografin (Meglumine diatrizoate; Schering) diluted 1–5 in normal saline	Known history of IV contrast allergy	Adrenaline, methylprednisolone and ICU admission
Joseph et al. USA 2021	Retrospective cohort study	No data	1000 patients, $RR = 0 (n = 0)$	RPG, PCNG, PCNL, URS	Steroid given to 45% ($n=39$) of patient with previous IV IC reaction	Iothalamate meglumine (conray)	No data	No data

Note: Reaction Rates are only calculated when the number of patients > 100.

No data: information isn't mentioned in articles or mentioned as 'couldn't be assessed'.

Abbreviations: APG, antegrade pyelogram; BL, bilateral; CG, cystogram; CS, cystoscopy; CUG, cystourethrogram; PCN, percutaneous nephrostomy; PCNG, percutaneous nephrostogram; BL, bilateral; CG, cystogram; CS, cystoscopy; CUG, cystogram; PCN, reaction rate; TURBT, trans urethral resection of bladder tumour; URG, urethrogram; URS, ureteroscopy; VCUG, voiding cystourethrogram; VUR, vestioureteral reflux.

*Pateitoris showed a significantly higher percentage in the AR group compared to the non-AR group (p <0.05). However, multivariate analysis indicated that a history of previous contrast reactions did not significantly increase the risk of urinary contrast reactions (Odds Ratio [OR]: 1.5; 95% Confidence Interval [CI], 0.9–2.8; p=0.2).

*PC: iodinated contrast, does not mention which type in specific.

Endourological Society, two cross-sectional retrospective reviews, one case report followed by a retrospective review, one retrospective cohort study, and four letters to the editor. Notably, two letters described the same case, so one was excluded, leaving 13 articles summarised in Table 1.

4.1 | Urological Procedures

The identified publications covered a variety of urological procedures involving IC. These included retrograde pyelogram, antegrade pyelogram, cystoscopy (with or without biopsy), cystogram, voiding cystourethrogram, percutaneous nephrostomy, nephrostogram, percutaneous nephrolithotomy, ureteroscopy (with or without stenting), retrograde urethrography, and voiding urodynamics, which involve retrograde bladder contrast with fluoroscopy.

4.2 | Clinical Presentations

Clinical presentations of urinary IC ARs exhibited significant variability, ranging from life-threatening anaphylaxis to mild skin rashes. ARs primarily affected three systems: skin, respiratory, and circulatory, with varying severity in each case. Skin symptoms included mild urticaria and severe angioedema. Respiratory symptoms ranged from mild wheezing to severe respiratory distress, such as laryngeal oedema, laryngospasm, pulmonary oedema, and dyspnoea. Circulatory symptoms varied from mild hypotension and arrhythmias to shock.

Most reactions were mild, with urticaria being the most common symptom. Over 50% of responding urologists reported seeing this presentation [3]. In a cross-sectional retrospective review, 87% (n = 342) of patients who experienced ARs to intra-urinary contrast presented with mild reactions, such as urticaria or mild hypotension [4]. However, in smaller studies like case reports and letters to the editor, 6 articles involved more severe anaphylactoid reactions [5–11].

4.3 | Rate of Allergy

In general, the incidence of allergic reactions is low, particularly in studies with larger sample sizes. In two retrospective studies with populations exceeding 10,000, the reported rates of allergic reactions were 0% and 0.48%, respectively [4, 12] Similarly, in three studies with sample sizes of approximately 1000, the highest reported incidence of allergic reactions was 4.2% [13].

Despite the relatively low incidence in the general population, allergic reactions are not uncommon. A 2018 web-based survey reported that 50.5% of responding urologists had encountered at least one allergic reaction during their professional careers [3].

4.4 | Pre-Medication

The administration of prophylactic medications, including the type, dosage, timing, and selection of patients, remains highly uncertain, with notable variability across institutions and individual practices.

The protocols for pre-medication appear to differ significantly, and the quality of available data from existing literature is generally low. Nearly half of the reviewed studies do not provide information regarding pre-medications. Even when pre-medication is mentioned, it is often described in a non-specific manner. For instance, in one cross-sectional retrospective review, 31% (n = 35) of patients with a history of IV IC reactions were reported to have received steroids or antihistamines as pre-medication [13]. However, no details were provided regarding the specific drugs, dosages, or timing of administration. Only one case report specified a regimen in which steroids were administered 13, 7, and 1 h before the procedure, along with 50 mg of Diphenhydramine 1 h prior [6]. However, this report involved only a single patient, limiting generalisation of the effectiveness of this approach.

Additionally, while it is widely accepted that pre-medication with steroids or antihistamines effectively prevents IV contrast reactions, the effectiveness of pre-medication for preventing ARs to urinary contrast agents remains unclear, as anaphylactic reactions were reported despite the use of pre-medication in some patients [6, 9, 10, 14].

4.5 | Type of Contrast Agents

Data on contrast agents used in the reviewed studies are notably limited. Of the 13 articles, one did not mention the contrast agent at all, and four merely referred to the use of IC without providing additional details such as the specific type of contrast, volume administered, or injection pressure during administration.

The remaining articles focused on two categories of contrast agents. Ionic contrast agents, such as Cysto-Conray (iothalamate sodium/meglumine) and Urographin (diatrizoate sodium/meglumine), are characterised by their high osmolality, which is five to eight times that of serum, and are associated with a higher incidence of ARs. In contrast, low-osmolality non-ionic contrast agents, with osmolality less than three times that of human serum, such as Omnipaque (iohexol), are preferred in modern practice for intravascular and intrathecal use due to their lower risk profile [15]. In general, studies conducted after the year 2000 more frequently utilised non-ionic contrast agents, while older studies tended to employ ionic agents. Additionally, some studies reported diluting the contrast with saline prior to administration in certain patients [6, 12].

4.6 | Predisposing Factors

Certain patient-related factors have been identified as potentially associated with an elevated risk of ARs to urinary IC. These factors include advanced age and the presence of comorbidities, such as hypertension, type 2 diabetes, congestive heart failure, coronary artery disease, chronic lung disease, and asthma. Additionally, suspected urinary infections, haematuria, or bleeding during the procedure, vesicoureteral reflux,

urothelial trauma, and bladder cancer have also been implicated as risk factors [3, 4, 12, 16].

Factors related to the contrast medium, such as the high volume, concentration, and injection pressure of the contrast agent, as well as the use of older generation contrast agents (high-osmolarity and ionic) and delayed urinary drainage, have been positively correlated with an increased risk of urinary IC ARs [3, 13, 16].

The role of a previous history of IV IC reactions in predicting urinary IC allergies remains uncertain. While the incidence of a history of previous contrast allergy was found to be 3% in the urinary contrast allergy group, compared to 1% in the nonurinary allergy group ($p\!=\!0.006$), multivariate analysis showed that a history of previous contrast reaction did not significantly increase the risk of urinary contrast reactions (Odds Ratio [OR]: 1.5; 95% Confidence Interval [CI], 0.9–2.8; $p\!=\!0.2$) [4]. Additionally, ARs related to urinary contrast have been documented in patients both with and without a known history of IV contrast allergy [5, 6, 8, 9].

4.7 | Management

The data regarding the management of urinary contrast allergies are scarce, with standardised protocols not being universally adopted. Nearly half of the reviewed articles did not mention any established management plans, which is particularly notable in large-scale retrospective reviews where such information would have been very valuable.

Among the available data, most stemming from case reports, the management were typically aligned with the clinical presentation and the severity of the reaction. Mild reactions often resolved spontaneously without intervention, while severe cases required intensive care unit (ICU) admission and intubation. Treatment generally involved supportive care and symptomatic management. Oxygen supplementation was provided in cases of hypoxia, and intravenous fluids or vasopressors were administered for hypotension. Pharmacologic interventions, including corticosteroids, antihistamines, and adrenaline, were used to counteract the allergic response.

5 | Discussion

ARs to non-intravascular IC, including those used in gastro-intestinal, hysterosalpingographic, and urological procedures, have been relatively underreported in clinical practice, despite their occurrence not being uncommon [17]. Our case report draws attention to urinary IC ARs, a topic that remains inadequately explored in current literature. Despite the scarcity of studies, the available evidence involves nearly all common urological procedures involving IC.

The clinical manifestations vary widely between individuals. In the case described, the allergic reaction presented as unilateral eye redness, swelling, itching, and photophobia, which had not been reported in previous literature. However, most reported reactions involve the skin, respiratory, and circulatory systems, either singly or in combination.

Patients with urinary contrast exposure presenting with suspicious symptoms should be promptly evaluated and managed. Although the overall incidence remains low and predominantly mild, severe cases, including anaphylaxis requiring intubation and ICU admission, have been documented. There were no fatal ARs reported.

It has traditionally been assumed that patients with an IV contrast allergy history are more prone to developing urinary contrast allergies. Interestingly, a study has challenged this assumption, suggesting no significant correlation between the two. Similarly, while pre-medication is commonly believed to help prevent allergic reactions, there was no evidence identified to support this.

One of the primary limitations of this systematic review is the limited amount of published data, which makes it challenging to draw reliable and generalisable conclusions. Additionally, publication bias must be considered, especially for case reports, given that cases with significant reactions are more likely to be published, potentially leading to an overestimation of the severity of ARs in systematic reviews. Another limitation of the existing literature is the variability in data collection across studies. Some articles focus primarily on documenting allergic symptoms without providing details on management strategies, while others thoroughly describe treatment protocols but omit information on pre-medication [18]. This inconsistency makes it challenging to compare data on the same level across studies. Moreover, within individual articles, the relationship between variables is often unclear. For example, in one study, it was reported that nearly one-third of patients received pre-medication, and the overall allergic reaction rate was 4.2% [13]. However, the study did not specify the number of patients who experienced allergic reactions who had received pre-medication, making it difficult to assess the effectiveness of pre-medication in preventing ARs.

Future research should prioritise the expansion of highquality studies with comprehensive and standardised data collection. Specifically, more investigations are needed to evaluate the efficacy of pre-medication as a prophylactic measure. If demonstrated to be effective, standardised protocols for its administration should be established. Additionally, further research into predisposing factors is critical for identifying high-risk patients, allowing for early risk stratification and prevention. Finally, the establishment of a standardised guideline for the management of urinary IC ARs is urgently needed.

6 | Conclusion

The incidence of adverse reactions to intra-urinary contrast agents is generally low and mild, although life-threatening cases have been documented. The clinical presentation of these reactions can vary significantly between individuals, complicating diagnosis. The lack of standardised treatment

protocols limits the effectiveness of clinical management. Additionally, the uncertainty surrounding predisposing factors impedes the development of clear preventive strategies. Further research is essential to address these challenges and improve patient safety in urological procedures involving contrast agents.

Author Contributions

S.X.: Conducted the literature search, article selection, data extraction, data review, summarisation, initial manuscript writing, table and figure revision, manuscript revision, and submission. N.W.: Contributed to data review, summarisation, manuscript review, and revision. L.W.: Conducted the literature search, article selection, data extraction, data review, summarisation, initial manuscript review, and assisted with submission. J.D.: Participated in article selection, data extraction, data review, summarisation, and table and figure creation. A.C.: Supervised the research and provided guidance throughout the study. N.W. and L.W. contributed equally. All authors read and approved the final manuscript.

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Ethics Statement

The authors have nothing to report.

Consent

Consent for the case report cannot be obtained as the patient is deceased.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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