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**Citation for published version:**

Di Cicco, MF, Fetzer, T, Secoura, PL, Jermyn, K, Hill, T, Chaloub, S & Vaden, S 2013, 'Management of bilateral idiopathic renal hematuria in a dog with silver nitrate' *The Canadian veterinary journal. La revue vétérinaire canadienne*, vol 54, no. 8, pp. 761-4.

**Link:**

[Link to publication record in Edinburgh Research Explorer](#)

**Document Version:**

Publisher final version (usually the publisher pdf)

**Published In:**

The Canadian veterinary journal. La revue vétérinaire canadienne

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# Case Report Rapport de cas

## Management of bilateral idiopathic renal hematuria in a dog with silver nitrate

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**Abstract** – Renal hematuria has limited treatment options. This report describes management of bilateral idiopathic renal hematuria in a dog with surgically assisted installation of 0.5% silver nitrate solution. Initial treatment resulted in freedom from clinical signs or recurrent anemia for 10 months; however, recurrence of bleeding following a nephrectomy resulted in euthanasia.

**Résumé** – Gestion de l'hématurie rénale idiopathique bilatérale chez un chien à l'aide du nitrate d'argent. L'hématurie rénale offre des options de traitement limitées. Ce rapport décrit la gestion de l'hématurie rénale idiopathique bilatérale chez un chien à l'aide de l'installation assistée par chirurgie d'une solution de nitrate d'argent de 0,5 %. Le traitement initial a produit une disparition des signes cliniques ou de l'anémie récurrente pendant 10 mois. Cependant, la récurrence des saignements après une néphrectomie se sont traduits par l'euthanasie.

(Traduit par Isabelle Vallières)

Can Vet J 2013;54:761–764

I diopathic renal hematuria is a diagnosis of exclusion, characterized by gross hematuria in the absence of an obvious source or mechanism for bleeding (1). Diagnosis requires direct visualization of the urinary tract via laparotomy, cystotomy, or cystoscopy as well as obtaining a sample of urine from each ureter. The incidence of unexplained renal hematuria in humans is estimated to be between 5% and 10% (2) and is believed to be uncommon in veterinary medicine.

Clinical signs vary from an incidental finding of microscopic or macroscopic hematuria to a severe anemia, ureteral and urethral obstruction, or death (3–6). Thirteen of the 17 cases reported in the veterinary literature were unilateral with a favorable outcome following nephrectomy (12/13) or benign neglect (1/13); however, the remaining bilateral cases resulted in death or euthanasia (1,4–8). The prevalence of bilateral involvement is unknown.

### Case description

An 11.5-year-old spayed female American Eskimo dog was referred to the Veterinary Health Complex, North Carolina State

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University (VHC NCSU) for gross hematuria of 1 mo duration. Previous assessments included laboratory evaluation [complete blood cell count (CBC), reticulocyte count, serum biochemistry profile, urinalysis, urine culture, prothrombin time, activated partial thrombin time, and buccal mucosal bleeding time], abdominal ultrasonography, and cystotomy. Abnormal results included a regenerative anemia [hematocrit (HCT) 23.4%, reference range (RR): 36% to 60%; reticulocytosis 207 000, reference value: < 6000; nucleated red blood cells (nRBC) 2/100 white blood cells (WBC)], decreased blood urea nitrogen (BUN); (1.4 mmol/L, RR: 2.5 to 9.6 mmol/L), increased alanine aminotransferase (ALT; 184 U/L, RR: 10 to 100 U/L), increased alkaline phosphatase (ALKP; 300 U/L, RR: 23 to 212 U/L), and hematuria [ $> 50$  RBC/high power field (hpf) reference value: 0]. Results of all coagulation tests were within the reference ranges. Findings during a focal urinary bladder ultrasound were consistent with, although not diagnostic for, a bladder wall mass. During cystotomy a thickened, hyperemic urinary bladder wall and a 2 to 3 cm dark red mass were found. Results of histopathologic evaluation of the mass were consistent with a blood clot.

On presentation to the VHC NCSU, the dog was quiet, alert, and responsive with a grade II/VI left basilar systolic heart murmur, bounding femoral pulses, and a healing ventral midline incision. Results of a CBC and limited biochemical panel disclosed a regenerative anemia (HCT 22.7%; 385 000 reticulocytes, reference value: < 6000), monocytosis ( $1.075 \times 10^3/\text{UL}$ , RR: 0.075 to  $0.85 \times 10^3/\text{UL}$ ), decreased creatinine (53.0  $\mu\text{mol/L}$ , RR: 61.9 to 132.6  $\mu\text{mol/L}$ ), hypoalbuminemia (29 g/L, RR: 30 to 39 g/L), and decreased bicarbonate (17 mmol/L, RR: 18 to 25.8 mmol/L). Ultrasonography of the urinary tract revealed a thickening of the cranioventral bladder wall, attributed to the previous cystotomy. The bladder lumen

contained layered hyperechoic material consistent with blood clots. Both kidneys contained small cortical cysts, and had normal vasculature and flow; kidney sizes were within the reference range (RR: 3.2 cm to 6.4 cm for dogs weighing 5 to 14 kg). Three-view thoracic radiographs were normal. The dog received a packed red blood cell (pRBC) transfusion (10 mL/kg BW over 3 h) without complication. Twelve hours after transfusion the packed cell volume (PCV) and total solids (TS) were 30% (RR: 39% to 53%) and 60 g/L (RR: 60 to 80 g/dL), respectively.

The following day cystoscopy [using a 2.1 mm rigid Karl Storz cystoscope (Karl Storz GmbH & Co. KG, Tuttlingen, Baden-Württemberg, Germany)] was performed while the dog was anesthetized pre-anesthetic medication included hydromorphone (Hydromorphone HCl; Baxter Healthcare, Deerfield, Illinois, USA), 0.1 mg/kg body weight (BW), IM; induction with propofol (Propofol; Abbott Laboratories, North Chicago, Illinois, USA), 6 mg/kg BW, IV; general anesthesia was maintained with inhaled isoflurane (Isoflurane; Piramal Healthcare, Piramal Critical Care, Bethlehem, Pennsylvania, USA) and oxygen.

The ureteral orifices were normal in appearance and clear to yellow jets were visualized from each. The portion of the bladder mucosa that was visualized appeared normal and there was no evidence of overt bleeding, although complete visualization of the entire bladder mucosa was precluded due to the presence of large consolidated blood clots. Because a cause of the severe hemorrhage had not been identified and the large blood clots that were preventing complete visualization of the bladder wall could not be removed during cystoscopy, a second cystotomy was done (9). Several large blood clots were extracted from the urinary bladder and clear urine was visualized from both ureters. The urinary bladder and ureters were grossly normal. A bladder wall biopsy was collected prior to closing in a simple continuous and Cushing's pattern using 3-0 PDS (PDS-II: 3-0; Ethicon, Somerville, New Jersey, USA). The linea alba was closed in a simple continuous pattern using 2-0 PDS (PDS-II:23-0; Ethicon), the subcutaneous layers in a continuous horizontal mattress pattern with 3-0 PDS, and the skin was apposed with adhesive tissue glue (Vetbond Tissue Adhesive; 3M Health Care, St. Paul, Minnesota, USA). Bladder wall histopathology revealed mild chronic multifocal mucosal hyperplasia.

Post-operative care included 0.45% NaCl (0.45% NaCl; Abbott Laboratories), 60 mL/kg BW/day, supplemented with potassium chloride (Potassium chloride; Hospira, Lake Forest, Illinois, USA), 0.05 mEq KCl/kg BW/h, fentanyl (Fentanyl; Hospira) continuous rate infusion (CRI), 3 µg/kg BW/h, and amoxicillin-clavulanic acid (Clavamox; Pfizer Animal Health, New York, New York, USA), 13.75 mg/kg BW, PO, q12h.

The following day the dog was bright, alert, and responsive. A repeat CBC disclosed a regenerative anemia (HCT 23.3%, 262 000 reticulocytes), thrombocytosis ( $469 \times 10^3/\text{UL}$ , RR: 190 to  $468 \times 10^3/\text{UL}$ ), leukocytosis ( $14.49 \times 10^3/\text{UL}$ , RR 4.39 to  $11.61 \times 10^3/\text{UL}$ ), mature neutrophilia ( $13.62 \times 10^3/\text{UL}$ , RR: 2.84 to  $9.11 \times 10^3/\text{UL}$ ), and lymphopenia ( $0.580 \times 10^3/\text{UL}$ , RR: 0.59 to  $3.30 \times 10^3/\text{UL}$ ). A transdermal fentanyl patch (Fentanyl Transdermal System; Corium International, Grand Rapids, Michigan, USA), (50 µg) was placed and iron dextran (Iron

Dextran; Phoenix Pharmaceuticals, St. Joseph, Missouri, USA), 10 mg/kg BW, IM, was administered. Prior to discharge the next day the dog was noted to have 1 episode of passage of discolored, red urine. The dog was discharged from the hospital with a presumptive diagnosis of idiopathic renal hematuria and instructions to be given tramadol (Tramadol HCl; Amneal Pharmaceuticals, Glasgow, Kentucky, USA), 2 mg/kg BW, PO, q8h, ferrous sulfate (Ferrous sulfate; Plus Pharma, Commack, New York, New York, USA), 8 mg/kg BW, PO, q24h, amoxicillin-clavulanic acid, a transdermal fentanyl patch (50 µg/h) and famotidine (Famotidine; Baxter Healthcare), 1 mg/kg BW, PO, q12h.

The dog was taken to the referring veterinarian 2 d after discharge for malaise, pollakuria, and stranguria with passage of large blood clots. Focal urinary bladder ultrasound revealed multiple blood clots and a worsening anemia with PCV and TS of 20% and 65 g/L, respectively.

On return to VHC NCSU the dog's physical examination was unchanged from previous assessments. On initial assessment the PCV and TS were 19% and 64 g/L, respectively. A major cross match was completed prior to a transfusion of packed RBC (10 mL/kg BW over 3 h). Twelve hours later PCV and TS were 27% and 50 g/L, respectively.

A cystoscopy was repeated under general anesthesia (premedication, induction, and general anesthesia as previously described) revealing large organized blood clots and discolored urine jets from the right ureteral orifice. The dog was transferred to surgery for an exploratory laparotomy and cystotomy. Intraoperatively the ureters were catheterized towards the kidneys with a 3 French red rubber catheter (3 French red rubber catheter; Kendall Sovereign Feeding Tube + Urethral Catheter, Tyco Healthcare, Mansfield, Massachusetts, USA). The left ureter revealed gross hematuria. Urine from the right catheter was grossly normal and was collected for urinalysis which revealed microscopic hematuria ( $> 50 \text{ RBC/hpf}$ ). A 0.5% silver nitrate solution (0.5% silver nitrate solution; Teva Pharmaceuticals, Sellersville, Pennsylvania, USA) was filtered with a 0.2 µm nylon membrane filter prior to injecting 1.5 mL into the left renal pelvis via the ureteral catheter. The left ureter was manually occluded for approximately 15 min. The left renal pelvis was flushed with 10 to 15 mL of sterile 0.9% NaCl (Hospira). The bladder and body wall closure and post-operative care were as previously described.

The following day a transdermal fentanyl patch (50 µg/h) was placed and maintenance fluids (0.45% NaCl) were halved (30 mL/kg BW/day). A limited biochemical panel disclosed a decreased BUN (1.1 mmol/L), decreased creatinine (44.2 µmol/L), hypocalcemia (2.2 mmol/L, RR: 2.3 to 2.9 mmol/L), hypoalbuminemia (25 g/L), hyperchloremia (124 mmol/L, RR: 108 to 122 mmol/L), and decreased bicarbonate (17 mmol/L, RR: 18 to 25.8 mmol/L). The PCV and TS remained stable at 34% and 64 g/L, respectively. The dog had one episode of passage of light pink-colored urine. A second limited biochemical panel disclosed hypoalbuminemia (29 g/L), and mild hyperkalemia (5.7 mmol/L, RR: 4 to 5.3 mmol/L). At the time of discharge, the urine was grossly normal and medications were as previously described.

The dog was re-evaluated 1 wk after surgery by the referring veterinarian. The PCV and TS were 37% and 72 g/L,

respectively. A focal urinary bladder ultrasound revealed a ventrally thickened bladder wall with minimal luminal debris. Urine via cystocentesis was cloudy with a pH of 5.0 (RR: 5.5 to 7.0), and hematuria (RBC > 50, RR: 0 to 3 RBC/hpf).

One month after surgery, the owner reported no evidence of gross hematuria or other clinical abnormalities and the PCV and TS were normal at 44% and 70 g/L. Urinalysis via cystocentesis disclosed grossly cloudy urine, and hematuria (21 to 50 RBC/hpf). The dog was administered yunnan baiyao (Yunnan baiyao; Activeherb Technology, San Diego, California, USA), 0.25 g, PO, q12h for persistent microscopic hematuria by the referring veterinarian.

Six months after surgery, a focal urinary ultrasound, urinalysis, biochemistry panel, and PCV/TS were repeated. Both kidneys were unchanged in size and vascular flow; the urinary bladder was thickened at the apex with small amount of luminal debris. Renal function appeared to be normal as assessed by results of a serum biochemistry panel (BUN 19 mmol/L, and creatinine 0.7 mmol/L). Urinalysis via cystocentesis disclosed light red urine and hematuria (RBC > 50 RBC/hpf). The PCV and TS were 48% and 80 g/L, respectively.

Ten months post-procedure the patient was presented with acute onset lethargy and with gross hematuria. The dog's physical examination was unchanged from previous assessments. Diagnostics included a CBC, limited biochemistry panel, and focal urinary tract ultrasound. Abnormal results included a regenerative anemia (HCT 29.1%; 165 000 reticulocytes), increased neutrophils with a left shift ( $17.16 \times 10^3/\mu\text{L}$ , RR:  $2.84$  to  $9.11 \times 10^3/\mu\text{L}$ ;  $1.54 \times 10^3$  band neutrophils) and decreased albumin (29 g/L). Ultrasound revealed a urinary bladder clot and mild left renal pelvic dilation with luminal hyperechoic debris. A laparotomy and cystotomy were repeated under general anesthesia (premedication, induction, and general anesthesia as previously described) revealing large organized blood clots in the bladder lumen. Both ureters were catheterized as previously described. A blood clot was palpated in the left renal pelvis. External digital manipulation and sterile saline flushes were repeated but did not dislodge the clot. The 0.5% silver nitrate solution was injected into the left renal pelvis via the ureteral catheter as previously described. The bladder, body wall closure, and post-operative care were as previously prescribed and the patient was discharged from the hospital 2 d after surgery. At discharge the urine was grossly normal with intermittent organized blood clots being passed.

One week following discharge the patient was taken to the referring veterinarian for recurrent gross hematuria and dysuria. A CBC disclosed a regenerative anemia (HCT 12.2%; 222 000 reticulocytes) and a mature neutrophilia ( $19.15 \times 10^3/\mu\text{L}$ ). Urinary bladder ultrasound confirmed large blood clots within the bladder lumen. The dog received a pRBC transfusion (10 mL/kg BW over 4 h) without complication prior to an exploratory laparotomy, selective arterial ligation (10) of the left renal artery and cystotomy. Active hemorrhage from either kidney was not present precluding arterial ligation. A left nephrectomy was performed as described elsewhere (11). The post-operative PCV was 22%. The kidney and renal pelvis were grossly normal in appearance. Histopathology of the left kidney revealed mild to moderate subacute neutrophilic

and lymphocytic pyelonephritis and ureteritis with nodular glomerular amyloidosis.

Two days after surgery, the dog required urinary catheterization due to urethral obstruction secondary to large blood clots. The PCV and TS were 16% and 50 g/L, respectively. A pRBC transfusion (10 mL/kg BW over 4 h) was repeated and 12 h post-transfusion the PCV and TS were 22% and 50 g/L, respectively. The dog was administered yunnan baiyao (frequency increased to 0.25 g PO, q8h) and methenamine (Urex; Vatriing Pharmaceuticals, Wytheville Virginia, USA) (10 mg/kg BW, PO, q6h). Gross hematuria, urethral obstruction, and blood loss anemia persisted for the next 24 h. The creatinine was increased (309 mmol/L) suspected secondary to a right ureteral obstruction evident on repeat urinary tract ultrasound. The dog was humanely euthanized with pentobarbital (Fatal Plus; Vertex Pharmaceutical, Cambridge, Massachusetts, USA), 1 mL/5 kg BW, IV, due to right renal hemorrhage that resulted in ureteral obstruction and subsequent azotemia. The right kidney was not obtained for histopathology.

## Discussion

This report describes surgically assisted instillation of aseptically filtered 0.5% silver nitrate solution into a renal pelvis with gross hemorrhage via a catheterized ureter. Following instillation, the ureter was manually occluded to ensure contact time and subsequent eschar formation. This procedure is different from protocols reported in the human literature which describe installation of a 0.25% to 1.0% solution through a ureteral catheter placed with cystoscopic guidance. The catheter remains *in situ* up to 3 d to allow for repeated instillations (12–14). Fluoroscopic-guided renal pelvic installation of silver nitrate has been performed in veterinary medicine with reported success and minimal complications (15).

Silver nitrate is a cauterizing agent that coagulates cellular protein resulting in an eschar (12) and cessation of hemorrhage. Installation of silver nitrate into the urogenital tract has been reported in the human literature for treatment of renal hematuria, bladder hemorrhage, and chyluria (12,13). Reported complications include flank pain, nausea, vomiting, hematuria, acute renal and hepatic failure, and necrotizing ureteritis but are uncommon (12–14).

The dog in this case exhibited intermittent bleeding with its severity resulting in a clinical anemia requiring multiple transfusions. Two cystoscopic procedures and a third cystotomy were initially required to confirm the kidneys as the source of the hemorrhage. The left kidney was determined to be the primary source of hemorrhage, urinary blood clots, and clinical anemia on the initial and subsequent evaluations; however, gross hemorrhage was visualized from the right ureter during cystoscopy prior to the patient's first treatment but was not repeatable at that time or on multiple gross examinations. An intra-operative urinalysis at the first treatment time revealed microscopic hematuria. The combination of these findings is indicative of intermittent hemorrhage from the right kidney. The possibility of catheter-induced trauma accounting for the microscopic hematuria exists but is thought to be less likely given the previous cystoscopic finding of gross hemorrhage. Given the bilateral



involvement on initial evaluation and concern for preservation of renal function, nephrectomy was not considered a viable treatment option. Both kidneys were not treated with silver nitrate simultaneously because there was concern that the silver nitrate could induce acute renal injury. Instead, the left kidney was chosen for treatment because that is the side that had gross hematuria during surgical exploration.

Ten months following the procedure, gross hematuria and blood loss anemia recurred. The left renal pelvic hematoma was suggestive that the left kidney was again the primary source of hemorrhage, and instillation of a 0.5% silver nitrate solution was repeated on the left side only. A urinalysis was not obtained from the right kidney to monitor for microscopic hematuria and the urine was grossly normal in appearance.

The transient response to the second instillation of silver nitrate could be a result of inadequate contact time and lack of eschar formation due to the large blood clot in the renal pelvis that could not be removed. Alternatively the presumed left-sided persistent bleeding could have resulted from the histologically confirmed subacute pyelonephritis rather than a recurrence of the idiopathic hemorrhage. The pyelonephritis was either bacterial, secondary to contamination during the recent surgical procedure, or an expected sterile inflammatory reaction to the silver nitrate solution. Urine was not cultured prior to instillation and it is possible that bacteria smaller than the size restriction of the nylon membrane present in the silver nitrate solution could have been introduced during the procedure.

Gross examination of urine exiting the ureteral catheter at the time of second silver nitrate instillation and left-sided nephrectomy failed to reveal gross hemorrhage from either kidney. Given the known bilateral involvement as evident by gross hemorrhage visualized on cystoscopy prior to the first treatment and documented on urinalysis, it is plausible that the source of the continued bleeding was actually the right kidney that was not treated at any time with the silver nitrate solution. Due to the lack of knowledge regarding the long-term effects and safety of the silver nitrate solution and previous cessation of hemorrhage with unilateral treatment, bilateral simultaneous instillation was not considered to be a safe treatment option.

The dog was administered a urinary antiseptic agent, methenamine, prior to euthanasia. This compound is hydrolyzed to formaldehyde in the urine which may have pro-coagulation properties. The dog received the medication for less than 24 h prior to euthanasia and its efficacy could not be evaluated.

This case report demonstrates the importance of alternative treatment options for cases of idiopathic renal hematuria. As in this report, previous cases of bilateral renal bleeding resulted in death or euthanasia due to the lack of treatment options once a nephrectomy has been performed. The initial response to the chemical cauterization with silver nitrate was favorable and resulted in 10 mo without clinical signs or anemia.

The authors believe that the yunnan baiyao administered did not contribute to the dog's 10-month interval without gross hematuria. Following the initial treatment the dog was free of gross hematuria for 1 month before the yunnan baiyao was started by the referring veterinarian. The medication was

administered for persistent microscopic hematuria, which was documented to be occurring from the untreated right kidney and did not resolve on subsequent urinalyses. Additionally this medication at increased frequency failed to resolve right-sided gross hemorrhage following the dogs left nephrectomy. The efficacy of this agent in the treatment of idiopathic renal hematuria is unknown. Its contribution to controlling or preventing recurrence of gross hemorrhage after the initial treatment cannot be determined in this case.

The recurrence of blood loss anemia and documented blood clots in bladder and ureters bolsters the possibility that the right kidney was the source of the hemorrhage following the second silver nitrate treatment. Given the intermittent nature of the hemorrhage from either kidney and lack of grossly visualization at the time of the nephrectomy, it cannot be definitively stated that second silver nitrate treatment was unsuccessful.

Chemical cauterization with silver nitrate solution should be considered a viable option for treatment of severe idiopathic renal hematuria. This case report demonstrates resolution of clinical signs and anemia for 10 months following instillation of a 0.5% silver nitrate solution into a grossly hemorrhaging renal pelvis. The efficacy of subsequent silver nitrate treatments cannot be fully evaluated given the known bilateral involvement. Additional studies exploring the efficacy, safety, and long-term effects of renal pelvic silver nitrate instillation are warranted. *CWJ*

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