PAPER

A retrospective study of canine idiopathic renal haematuria: clinical findings and outcome following medical treatment

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Objectives: To characterise and document the progression of idiopathic renal haematuria in a large cohort of medically managed UK dogs.

Materials and Methods: Retrospective study of 41 client-owned dogs with confirmed (n=14), or suspected (n=27) idiopathic renal haematuria from 4 UK-based referral centres. Clinical findings and outcomes of dogs (2001 to 2018) were determined from the review of medical records and telephone follow-up.

Results: Median survival time from diagnosis was long [1482 (152 to 1825) days] irrespective of treatment and clinical response. Only 1 case was euthanased due to idiopathic renal haematuria, and anaemia or azotaemia occurred infrequently. In total, 25 dogs received angiotensin-converting enzyme-inhibitor or angiotensin receptor blocker therapy, of which 23 received benazepril [0.44 (0.19 to 0.82) mg/kg/24 hours], two received enalapril (0.40 and 0.78 mg/kg/24 hours) and one received telmisartan (1 mg/kg/24 hours). In cases with follow-up urinalyses, complete resolution of haematuria was documented in eight of 19 (42%) dogs following angiotensin-converting enzyme-inhibitor/angiotensin receptor blocker treatment, with partial improvement in five of 19 (26%) and no improvement in six of 19 (31%). Conversely, of the two untreated dogs where outcome was available, one had partial improvement and the other had no improvement.

Clinical Significance: In this study, idiopathic renal haematuria was associated with a good prognosis and low complication rate. Resolution or improvement in haematuria occurred in both angiotensin-converting enzyme-inhibitor/angiotensin receptor blocker-treated and untreated dogs, indicating that further studies are required to evaluate the effectiveness and safety of these interventions.

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INTRODUCTION

Idiopathic renal haematuria (IRH), or benign essential haematuria, is a rare cause of chronic and potentially severe blood loss. In both dogs and humans, it has been previously been defined as acute, intermittent, or chronic gross haematuria for which radiologic and haematologic evaluation reveals no source (Bagley & Allen 1990; Tawfiek & Bagley 1998; Berent *et al.* 2013; Berent & Weisse 2014). Therefore, diagnosis typically relies on exclusion of alternative aetiologies including trauma, urolithiasis, neoplasia, coagulopathy and urinary tract infection. Confirmation of upper urinary tract haemorrhage has historically necessitated surgically assisted ureteral catheterisation; however, the increased availability of cystoscopy has permitted minimally invasive confirmation and more definitive exclusion of urethral lesions (Stone *et al.* 1983, Holt *et al.* 1987, Berent *et al.* 2013, Berent & Weisse 2014, Adelman *et al.* 2017).

The cause of IRH in dogs remains poorly understood. In humans, haemorrhage is often attributed to vascular abnormalities, such as haemangiomas and angiomas of the renal papillae or pelvis (Rowbotham & Anson 2002, Dooley & Pietrow 2004, Tanimoto *et al.* 2017); however, in the largest study describing renal histopathology in IRH-affected dogs, this was confirmed in only one of nine cases, with the remaining eight cases having no clear aetiology (Holt *et al.* 1987). The advent of ureteropyeloscopy has recently led to the documentation of renal pelvic lesions with an appearance suggestive of angiomas in several dogs with IRH; however, their true prevalence in this species remains unknown and other aetiologies are potentially also possible (Tawfiek & Bagley 1998, Dooley & Pietrow 2004, Araki *et al.* 2012, Berent & Weisse 2014). In humans, haematuria is often related to glomerular disease (including IgA nephropathy, Alport syndrome and thin basement membrane disease), accounting for up to 66% of cases, and similar syndromes may therefore also exist in the dog (Kupor *et al.* 1975, Chester *et al.* 1978, Fairley & Birch 1982, Tapp *et al.* 1986, Rowbotham & Anson 2002, Yuste *et al.* 2015). Although glomerular haematuria is reportedly uncommon in dogs, this assumption is based on supposition rather than evidence. Abnormal urinary erythrocyte morphology and compatible renal histopathology often facilitate its diagnosis in people; however, this information in rarely available for dogs and interpretation of proteinuria is complicated by the coexistence of urinary haemorrhage (Fairley & Birch 1982, Yuste *et al.* 2015).

Due to the risk of anaemia, iron deficiency and ureteral or urethral obstruction, ureteronephrectomy was historically recommended for dogs with IRH (Stone *et al.* 1983, Hitt *et al.* 1985, Holt *et al.* 1987, Jennings *et al.* 1992, Hawthorne *et al.* 1998). Given the inevitable detriment to renal function and the high incidence of subsequent bilateral disease however, various other options have been investigated (Mishina *et al.* 1997, Berent *et al.* 2013, Di Cicco *et al.* 2013, Berent & Weisse 2014, Adelman *et al.* 2017). Most recently, two studies described the treatment of IRH with endoscopically assisted sclerotherapy (Berent *et al.* 2013, Adelman *et al.* 2017). Although this resolved gross haematuria in six of eight cases, this procedure requires specialist equipment, training and expertise, and is not widely available. Furthermore, although uncommon, renal pain has been reported in both humans and dogs following sclerotherapy, and other complications including vomiting, corrosive renal and ureteral injury, and renal dysfunction may potentially also occur (Goel *et al.* 2004, Berent *et al.* 2013). Interestingly, in the aforementioned study by Berent *et al.*, ureteropyeloscopy was performed in one of the two persistently haematuric dogs but failed to document a bleeding lesion, supporting the theory that other aetiologies may result in renal haematuria and have indistinguishable clinical signs (Berent *et al.* 2013).

Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor antagonists (ARBs) are commonly used for the management of glomerular proteinuria, acting by preferential dilation of the efferent glomerular arteriole and consequent reduction in intraglomerular pressure (Grauer *et al.* 2000, Brown *et al.* 2013). In addition, complex roles of angiotensin in the regulation of renal hemodynamics and medullary blood flow, and glomerular permselectivity have also been suggested (Chou *et al.* 1986, Cupples *et al.* 1988, Borchhardt *et al.* 1997, Bądzyńska *et al.* 2002, Sangalli *et al.* 2011). In humans, ACEi may be recommended for certain forms of renal haematuria (Hebert *et al.* 1996, Tojo *et al.* 2006, Kashtan *et al.* 2013). Given that the aetiology of IRH in dogs is poorly understood and no previous studies have investigated medical treatment options, the aim of this study was to better characterise the disease in a large number of conservatively managed dogs with confirmed or suspected IRH and to evaluate whether ACEi/ARB therapy is associated with improvement of haematuria.

METHODS

Hospital records from four UK-based veterinary referral institutions (one university and three private practices) were each retrospectively searched for cases with a final diagnosis of IRH. Searches and assessment of case eligibility were performed independently by a single operator from each institution (AJK, JB, ACCK, AGS, respectively). Clinical information regarding signalment, historical findings, previous treatment, physical examination findings, results of diagnostic investigations and treatment recommendations were derived from each case's medical records by each of the aforementioned operators and subsequently submitted as an anonymised Microsoft Excel spreadsheet to the primary investigator (AK) for collation and analysis. All diagnoses were made by a European or American board-certified specialist in small animal internal medicine following thorough diagnostic investigation performed at the discretion of the primary clinician. Decisions regarding treatment, including the type, dose and frequency of ACEi or ARB therapy, were dictated by clinician preference. Minimum inclusion criteria comprised persistent haematuria in the absence of an alternative underlying aetiology based on a combination of: clinical history, physical examination, haematology, serum biochemistry, complete urinalysis, urine culture, coagulation profile and abdominal imaging (including ultrasonography, radiography, intravenous urography, urethrocystography).

Cases were further divided into two subpopulations: those with confirmation of haemorrhage from the ureterovesicular junction (UVJ) (Group IRH-C); and those where renal haemorrhage was suspected based on exclusion other aetiologies (Group IRH-S). Cases with incomplete medical records, abnormalities on diagnostic evaluation suggestive of another possible aetiology for haematuria, or evidence of concurrent disease were excluded.

For each case meeting the inclusion criteria, follow-up data were obtained by contacting referring veterinary practices in order to determine response following treatment. Improvement of haematuria was defined as: "complete resolution" if subsequent urinalysis demonstrated resolution of macroscopic and microscopic haematuria; "partial improvement" if treatment was associated with reduction in the severity of gross haematuria but persistence of microscopic haematuria on repeat urinalysis; or "no improvement" if the magnitude of haematuria was considered unchanged. Details of adverse effects relating to ACEi treatment or disease progression, and results of subsequent clinicopathological investigations (haematology, biochemistry, urinalysis) were also recorded. Relapses of haematuria, either recorded on subsequent urinalyses or due to re-presentation for recurrence of gross haematuria, were also recorded.

Statistical analysis

Data analysis was performed on the entire data set (*i.e.* IRH-S + IRH-C) followed by sub-analysis of Groups IRH-C and IRH-S alone. Descriptive statistics were used to describe the signalment, clinical signs, clinicopathological and diagnostic imaging findings of the dogs with IRH, and to evaluate longitudinal progression of the disease and response following treatment. Survival time was defined as the time between diagnosis of IRH and death or euthanasia (all-cause mortality) and was investigated using Kaplan–Meier analysis. Survival times were compared between groups using the Log-rank test. Dogs that were alive or lost to follow up at the study end-point (December 2018) were censored from the survival analysis. Due to the low numbers of dogs per treatment and diagnosis group, and consequently low statistical power, further subgroup analyses were not performed.

Statistical analysis was performed using commercially available software (IBM SPSS Statistics v25 for Windows, IBM Corp, Armonk, New York and GraphPad Prism v6 for Windows, GraphPad Software, La Jolla, California) and $P < 0.05$ was considered statistically significant. Unless otherwise stated, data are presented as median (range), or number (percentage).

RESULTS

Patient population

In total, 41 dogs met the criteria for inclusion (2001 to 2018). Case selection, pertinent clinical data and outcomes are summarised in Fig 1 and Table 1. In total, 20 different breeds were represented, of which the most common were: cocker spaniels (seven cases), boxers (six cases) and Labrador retrievers (three cases). The median age was 4.5 years (3 months to 13.25 years). There were 24 male dogs (15 neutered, nine entire) and 17 females (11 neutered, six entire).

Gross haematuria was the primary presenting sign in 39 cases (95.1%), whereas haematuria was identified incidentally in two dogs (4.9%). Intermittent dysuria, attributed to voiding of blood clots, was additionally reported in four dogs (9.7%; two IRH-C and two IRH-S). Overall, 33 dogs had received treatment before referral following the onset of haematuria but with no significant improvement (Table S1). Clinical examination performed at the time of referral was unremarkable in all dogs, other than mild hyperthermia in one case (39.2°C), and blood pressure measurement was <160 mmHg or reported as within normal limits in the 11 cases where this information was available.

Clinicopathological findings

Haematology and biochemistry results were available for review in 37 of 41 and 36 of 41 cases, respectively, with no significant abnormalities reported in the remaining dogs. Median packed cell volume (PCV) or haematocrit (HCT) was 45% (21 to 59%) with eight of 41 dogs reported to have a mild or moderate anaemia (PCV/HCT 21 to 34%). This was considered to be regenerative in three cases, non-regenerative in two cases (all samples obtained >1 week after onset of haematuria), and was not specified in three cases. Microcytosis and hypochromasia, suggestive of iron deficiency, was documented in two dogs with moderate, non-regenerative anaemia (PCV/HCTs of 21 and 26%; one IRH-C and one IRH-S); however, serum iron quantification was not performed. Both cases had a chronic history of gross haematuria over the preceding 6 months.

Automated platelet counts were variable, ranging from 122×10^9/L to 543×10^9/L (median 273×10^9/L). Mild thrombocytopaenia was reported in four dogs but was not considered to be of sufficient severity to result in spontaneous haemorrhage. Prothrombin and activated partial thromboplastin times were recorded in 29 cases, buccal mucosal bleeding times in three, d-dimers concentration in three, von Willebrand's factor antigen concentration in two and *Angiostrongylus vasorum* serology in one case – all were considered within normal limits. Thromboelastography was performed in five cases and was reported as unremarkable in three and suggestive of mild hypercoagulability in two likely reflecting in vitro artefact due to anaemia.

Azotaemia, defined as an increase in serum urea or creatinine concentration exceeding the laboratory reference intervals, was generally uncommon although mild elevations in serum creatinine were noted in two dogs (140 and 182 µmol/L). In both cases, urine-specific gravity was sub-optimally concentrated, suggestive of a renal or post-renal origin. Other derangements in biochemical parameters were generally mild and non-specific (Table S2).

Urinalysis results were available for review in 36 dogs and reported as unremarkable, aside from haematuria, in the remaining five. A strongly positive heme reaction (4+) on dipstick evaluation and >50 erythrocytes per high power field (hpf) on sediment examination was documented in all samples and 72% (26/36) were noted to have red/brown discolouration. Median urine-specific gravity was 1.032 (1.010 to 1.050). All but one

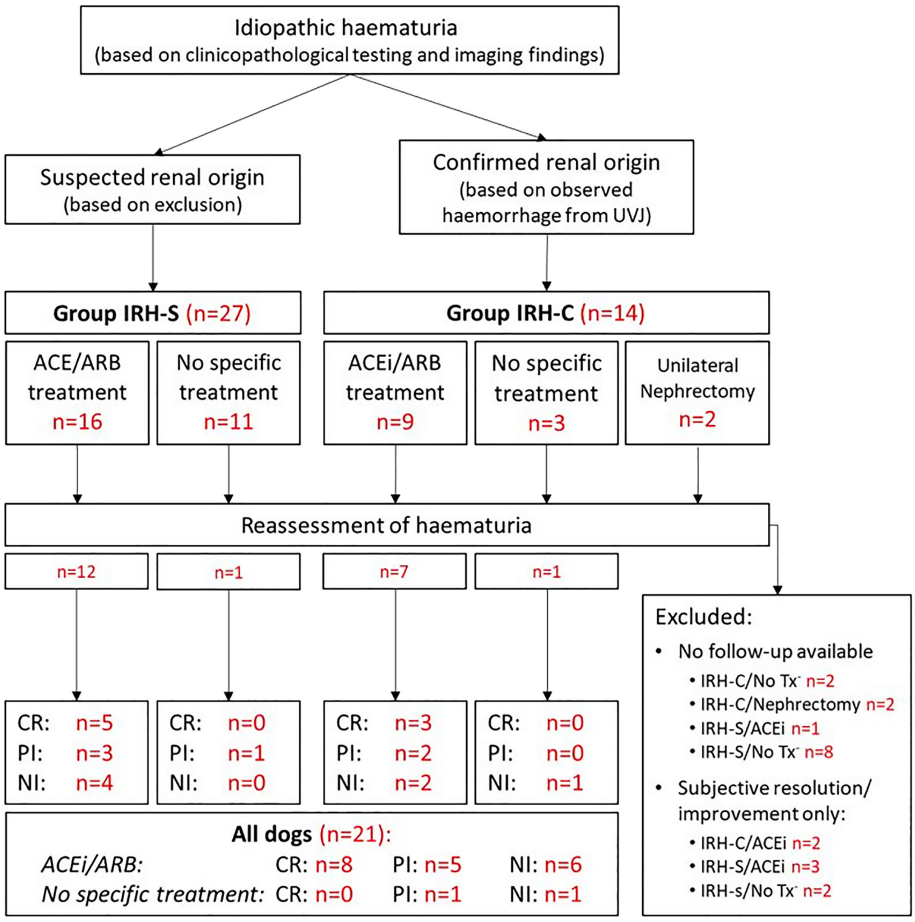

FIG 1. Flowchart illustrating case selection, subcategorisation, and outcomes following treatment. The study population was divided into cases with confirmed (Group IRH-C) or suspected (Group IRH-S) and further subdivided according to treatment. In cases where repeat urinalyses were available, change in haematuria was described as either complete resolution (CR), partial improvement (PI) or no improvement (NI). Outcomes for groups IRH-C, IRH-S and the overall study population are detailed at the bottom of the flowchart. The number of cases in each group that were excluded from the follow-up analysis, along with reasons for the exclusion, are also specified

dog had concurrent proteinuria on dipstick evaluation (1+ to 3+) with urine protein: creatinine ratios (UPC) ranging from 0.20 to 17.4 (median 1.50, n=27). Other than marked haematuria, analysis of urinary sediment was largely unremarkable except for occasional struvite crystals in three cases, rare granular casts in two cases and granular debris in one case. Pyuria was documented in only four dogs (median 25 cells/hpf; range: 20 to 90 cells/hpf) and bacterial culture results were negative in all cases.

Diagnostic imaging and endoscopic findings

Abdominal imaging was performed in all dogs, including abdominal ultrasound in 41 cases, radiography in 25, MRI in three and CT in two. Contrast imaging was undertaken in 24 dogs, including intravenous urography in 15 cases and retrograde urethrocystography in nine. Pyelectasia or ureteral dilation was documented in 10 cases with suspected blood clots within the renal pelvis or ureters in six dogs. In addition, structures consistent with clots within the urinary bladder were described in five dogs (three with concurrent renal or ureteral clots), and echogenic sediment within the urinary bladder was reported in a further 10 cases. Other than occasional small (<1 cm), thin walled, anechoic cysts within the renal parenchyma in three dogs, no other structural abnormalities were described.

Cystoscopy was performed in 17 dogs and haemorrhage from the UVJ was visualised in 11 cases. In the remaining six dogs, the ureteral jets were subjectively normal in appearance; however, the degree of haematuria at the time of cystoscopy was milder than at initial presentation and no other causative lesions were identified. IRH was therefore suspected, however ureteral catheterisation or repeat cystoscopy was not performed to confirm the diagnosis. In addition to those undergoing cystoscopy, upper urinary tract haemorrhage was also confirmed in three dogs by exploratory laparotomy and cystotomy. Overall, of the 14 dogs where gross haematuria from the UVJ was visualised, haemorrhage was unilateral in 11 (left-sided in five dogs, right-sided in four and unspecified in two), and bilateral in three dogs. No concurrent structural abnormalities or developmental malformations were reported in any cases.

Treatment

Twenty-five dogs were treated with an ACEi or ARB, 14 received no specific treatment and two dogs underwent unilateral

Table 1. Relevant clinical data and diagnostic abnormalities

	All dogs	Group IRH-C	Group IRH-S
Patient data (n)	41	14	27
Age (median [range] years)	4.5 (0.3 to 13.3)	2.8 (0.3 to 9.1)	5.2 (0.4 to 13.3)
Weight (median [range] kg)	22.4 (7.2 to 74)	20.5 (12 to 72)	23.5 (7.2 to 74)
MN/ME/FN/FE (n)	15/9/11/6	3/2/4/5	12/7/7/1
Common breeds (n)	Cocker spaniel (7) Boxer (6) Labrador (3)	Cocker spaniel (3) Boxer (2) Springer spaniel (2)	Cocker spaniel (4) Boxer (4) Labrador (2)
Haematology (n)†	37	12	25
PCV/HCT (median [range] %)	45 (21 to 59)	47 (24 to 52)	45 (21 to 59)
Prevalence of anaemia (%)‡	22	33	16
Platelets (median [range]×10^9/L)	273 (122 to 543)	315 (169 to 436)	250 (122 to 543)
Biochemistry (n)†	36	12	24
Serum urea concentration (median [range] mmol/L)	5.6 (1.2 to 10.4)	5.4 (4.1 to 10.4)	5.8 (1.2 to 10.3)
Serum creatinine concentration (median [range] µmol/L)	91 (49 to 182)	72 (49 to 113)	92 (51 to 182)
Prevalence of renal/post-renal azotaemia (%)‡	5	0	8
Urinalysis (n)†	36	10	26
Urine specific gravity	1.031 (1.010 to 1.050)	1.033 (1.028 to 1.045)	1.029 (1.010 to 1.045)
Urine protein: creatinine ratio	1.5 (0.2 to 17.4)	3.7 (0.5 to 8.7)	1.3 (0.2 to 17.4)
Prevalence of proteinuria (%)‡	97	100	96
Urine RBC (/hpf)	>50 in all dogs	>50 in all dogs	>50 in all dogs
Urine WBC (median [range]/hpf)	<5 (<5 to 90)	<5 (<5 to 90)	<5 (<5 to 50)
Bacterial culture	Negative in all dogs	Negative in all dogs	Negative in all dogs
Diagnostic imaging (n)	41	14	27
Prevalence of pyelectasia/ureteral dilation (%)‡	24	29	22
Prevalence of ureteral/pelvic blood clots (%)‡	15	14	15
Prevalence of urinary bladder blood clots (%)‡	12	21	7
Prevalence of echogenic urinary bladder sediment (%)‡	24	21	26

†Results were reported as unremarkable in remaining cases but unavailable for review
‡Prevalences based on population with data available for review

nephrectomy. Treatment with benazepril was recommended in 23 of 25 cases [median 0.44 mg/kg/24 hours (0.19 to 0.82 mg/kg/24 hours)] and enalapril in two dogs (0.40 and 0.78 mg/kg/24 hours, respectively). In one dog, treatment was initiated with benazepril but subsequently continued with telmisartan (1 mg/kg/24 hours). Indefinite treatment was recommended in seven cases, whereas treatment was discontinued after a median of 7.4 months (0.75 to 52 months) in the remaining 14 dogs where this information was available. In addition, 18 dogs concurrently received other therapies, including symptomatic treatments and antibiosis (Table S3); however, none received anti-androgen therapy or underwent castration.

Outcome and survival analysis

Follow-up haematology [152 (9 to 1879) days following diagnosis], and serum biochemistry analyses [38 (9 to 1878) days following diagnosis] were available in 15 cases, of which 13 had received ACEi/ARBs and two received no specific treatment. No adverse effects of ACEi/ARB treatment, such as elevation in creatinine, electrolytes abnormalities, gastrointestinal signs or incoordination/weakness, were documented. Irrespective of the severity of initial clinical signs or disease progression, no dogs developed azotaemia or sustained a deterioration in creatinine and only one patient (Group IRH-S) remained anaemic on repeat haematology analysis with PCV/HCT in the other cases remaining within normal limits. This dog was severely haematuric with a hypochromic non-regenerative anaemia (PCV/HCT 21%) on initial presentation, responded poorly to benazepril and tranexamic acid therapy, and was euthanased 150 days following diagnosis due to persistent haematuria and anaemia (PCV/HCT of 20%).

Response following treatment could be determined for 21 dogs (Fig 1), with results of one or more subsequent urinalyses [72 (6 to 1878) days following diagnosis] available in 19 cases, and two reported to have persistent, unchanged gross haematuria. Overall, of dogs receiving ACEi/ARB treatment (n=19), eight (42%) were considered to have complete resolution of both macroscopic and microscopic haematuria. Partial improvement occurred in five dogs (26%), and six (32%) had no improvement following treatment. Both dogs which additionally received tranexamic acid had either partial or no improvement. Of the dogs receiving no specific treatment (n=2), one had partial improvement and the other had no improvement. Due to the small number of untreated dogs and consequent lack of statistical power, further statistical analysis of these data was not performed.

Of the 14 dogs with complete resolution or partial improvement, only three were re-presented to their primary or referral veterinarian for recurrence or worsening of haematuria: two of these dogs had received ACEi/ARB therapy, one with complete and one with partial improvement; and the remaining dog was untreated but considered to have an initial partial improvement.

The median survival time for the total population (*i.e.* IRH-C + IRH-S, n=41) was 1482 (152 to 1825) days (Table 2). At the time of data collection, 21 dogs were still alive [median follow-up time 458 (49 to 2070) days] and 10 cases were lost to follow-up (eight at day 0, and two cases after 460 and 1228 days). The remaining 10 dogs were all euthanased with reasons cited in eight cases. Only one dog was euthanased due to persistent

Table 2. Survival data for the total study population and for subgroups IRH-C and IRH-S. For each respective group, data is reported for all dogs and for subpopulations stratified by treatment (ACEi/ARB or no specific treatment) or response following treatment

	All dogs			Group IRH-C			Group IRH-S		
	Median (range) survival time	Total/censored cases	Sig.	Median (range) survival time	Total/censored cases	Sig.	Median (range) survival time	Total/censored cases	Sig.
All	1482 (152 to 1825)	41/31	N/A	1482 (834 to 1482)	14/12	N/A	1412 (152 to 1825)	27/19	N/A
ACEi/ARB treatment	1412 (152 to 1412)	25/19	0.81	834 (834)	9/8	0.81	1412 (152 to 1412)	16/11	0.75
No specific treatment	1825 (171 to 1825)	16/12		1482 (1482)	5/4		1825 (171 to 1825)	11/8	
Complete resolution	834 (182 to 834)	8/6	P>0.05 for	834 (834)	3/2	P>0.05 for	ND† (182)	5/4	P>0.05 for
Partial improvement	ND† (152)	6/5	all group	ND†	2/2	all group	ND† (152)	4/3	all group
No improvement	1482 (1412 to 1482)	7/5	comparisons	1482 (1482)	3/2	comparisons	1412 (1412)	4/3	comparisons
No data	1252 (273 to 1825)	20/15		ND†	6/6		1252 (273 to 1825)	14/9	

†Not determined (survival point not reached)

haematuria, with all other cases related to other unrelated disease conditions or poor quality of life associated with old age. Overall, there was no significant difference in survival times of dogs treated with ACE-I/ARBs [1412 (152 to 1412) days] and those that were untreated [1825 (171 to 1825); P=0.81, Fig 2]. There was also no significant difference in survival times of dogs stratified by response following treatment [complete resolution 834 (182 to 834) days; partial improvement median survival time not reached (152); no improvement 1482 (1412 to 1482); response not recorded 1252 (273 to 1825) days; all P values >0.05].

Sub-analysis of group IRH-C

Of the 41 included dogs, 14 had visually confirmed haemorrhage from the UVJ (Group IRH-C). On sub-analysis of Group IRH-C, signalments, presenting signs, and clinicopathological and diagnostic imaging findings of IRH-C cases were similar to those for Group IRH-S and the total study population (Table 1). Cocker spaniels (three cases), boxers (two cases) and springer spaniels (two cases) were most commonly represented. Of the 14 dogs, eight received benazepril [0.41 mg/kg/24 hours (0.21 to 0.60)] and one received enalapril (0.78 mg/kg/24 hours), with treatment continued indefinitely in two, and discontinued after a median of 5.0 months (0.75 to 15) in the remaining seven dogs. The remaining five of 14 received no specific treatment.

Where outcome could be ascertained, complete resolution of haematuria was documented in three of seven (43%) ACEi/ARB-treated cases, with partial improvement in two of seven (29%) and no improvement in two of seven (29%) (Fig 1). Only one dog, with initial partial improvement, was subsequently represented with haematuria. Of the five untreated dogs, response could be determined in only one which displayed no improvement.

Survival information was available for nine cases of which seven were still alive at the time of data collection with a median follow-up time of 543 (122 to 1846) days (Table 2). Of the two dogs which died, one achieved a complete response following ACEi treatment but was euthanased after 834 days due to a subsequent diagnosis of multicentric lymphoma. The other case received no specific treatment and continued to have recurrent episodes of gross haematuria but was only ultimately euthanased after 1482 days as a consequence of acute-onset dyspnoea. There was no significant difference in survival between ACEi/ARB and untreated dogs (P=0.81, Fig 3, Table 2), or in survival times of dogs stratified by response following treatment (P >0.05 for all comparisons, Table 2).

Sub-analysis of group IRH-S

Of the 41 included dogs, 27 were diagnosed based on the exclusion of other aetiologies (Group IRH-S). Signalments, presenting signs, and clinicopathological and diagnostic imaging findings of IRH-S cases were also similar to those for Group IRH-C and the total study population (Table 1) with cocker spaniels (four cases), boxers (four cases) and Labrador retrievers (two cases) most commonly represented. Fifteen dogs received benazepril [0.46 mg/kg/24 hours (0.19 to 0.82)], one of which was subsequently treated with telmisartan (1 mg/kg/24 hours), and one received enalapril (0.40 mg/kg/24 hours). Treatment was continued indefinitely in five cases

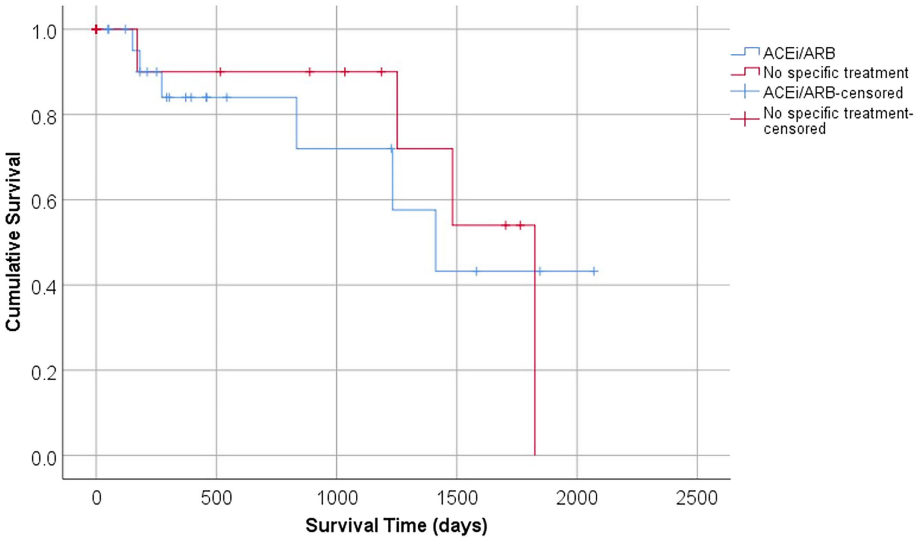

FIG 2. Kaplan–Meier survival analysis of the total study population (*i.e.* IRH-C and IRH-S groups combined), stratified by treatment (n=41). Survival times were compared between groups using the log rank test. Dogs that were alive or lost to follow up at the time of data collection were censored from the analysis (n=31). Median survival times were not significantly different between ACEi/ARB and untreated dogs (1412 days *versus* 1825 days, respectively; P=0.811)

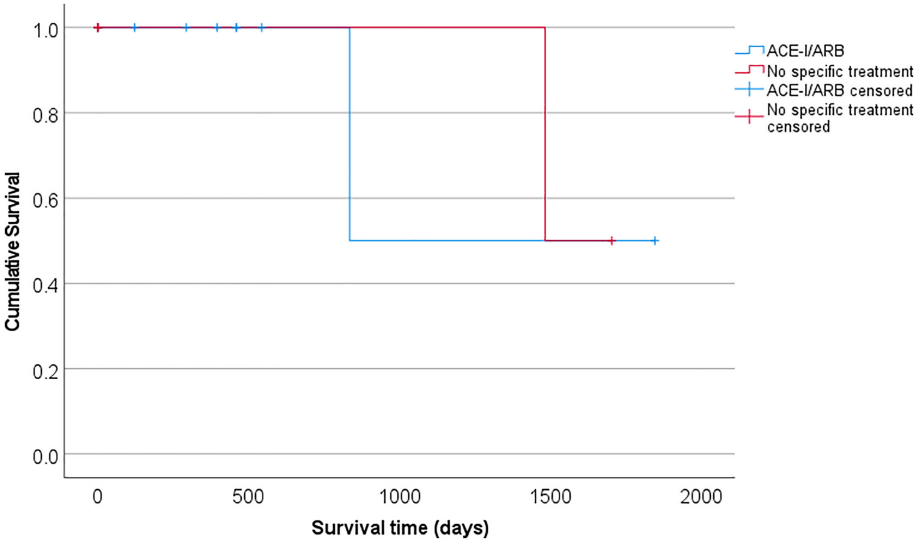

FIG 3. Kaplan–Meier survival analysis of dogs in Group IRH-C stratified by treatment (n=14). Survival times were compared between groups using the log rank test. Dogs that were alive or lost to follow up at the time of data collection were censored from the analysis (n=12). Median survival times were not significantly different between ACEi/ARB and untreated dogs (834 days *versus* 1842 days, respectively; P=0.808)

and discontinued after a median of 9.5 months (0.75 to 52) in the remaining eight dogs where this information was recorded. The remaining 12 cases received no specific treatment.

Where outcome could be determined, complete resolution of haematuria was documented in five of 12 (42%) ACEi/ARB-treated cases, partial improvement in three of 12 (25%), and no improvement in four of 12 (33%) (Fig 1). Follow-up was available for only one untreated dog which was considered to have had partial improvement. Relapse was reported in only this case and in one other dog which had previously experienced complete resolution of haematuria following enalapril therapy.

Median survival time for Group IRH-S was 1412 (152 to 1825) days (Table 2). Fourteen dogs were still alive at the time of data collection [median follow-up time 445 (49 to 2070) days] and five cases were lost to follow-up (4 at day 0, and 1 after 1228 days). The remaining eight dogs were all euthanased with only one as a consequence of persistent haematuria. Survival times were not significantly different irrespective of treatment (P=0.75, Fig 4, Table 2), or response following treatment (P > 0.05 for all comparisons, Table 2).

DISCUSSION

In both Group IRH-C and Group IRH-S in this study, dogs diagnosed with IRH had long survival times irrespective of treat-

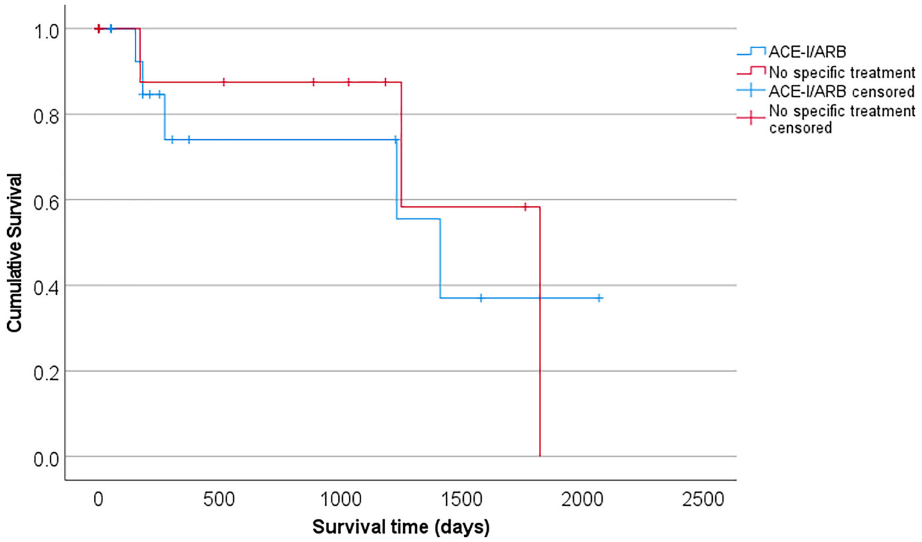

FIG 4. Kaplan–Meier survival analysis of dogs in Group IRH-S stratified by treatment (n=27). Survival times were compared between groups using the log rank test. Dogs that were alive or lost to follow up at the time of data collection were censored from the analysis (n=19). Median survival times were not significantly different between ACEi/ARB and untreated dogs (1412 days *versus* 1852 days, respectively; P=0.750)

ment and were often euthanased for reasons unrelated to IRH or progression of renal disease. Furthermore, longitudinal follow-up of these cases suggested that the development of anaemia or renal azotaemia were rare occurrences, even in cases with persistent haematuria. Many ACEi/ARB-treated dogs had either complete resolution of both gross and microscopic haematuria [eight of 19 (42%) in the overall population or three of seven (43%) in Group IRH-C] or partial improvement [five of 19 (26%) in the overall population or three of seven (29%) in Group IRH-C] on reassessment. Conversely, haematuria persisted in both of the untreated dogs with ascertainable outcome; however, the partial improvement in one of these cases (Group IRH-S) raises the possibility that spontaneous improvement may also occur in a subset of dogs.

Similar to previous reports, dogs in this study were generally young to middle aged (median 4.5 years), otherwise healthy, and typically presented following the development of gross haematuria. Concurrent dysuria, attributed to voiding of blood clots or obstructive uropathy, also occurred in minority of patients, as previously described (Stone *et al.* 1983, Hitt *et al.* 1985, Holt *et al.* 1987, Mishina *et al.* 1997, Berent *et al.* 2013). However, the predilection for large breeds in the previously cited studies was not evident and, instead, cocker spaniels and boxers appeared commonly in our dataset (seven of 41 and six of 41 in the overall population; and three of 14 and two of 14 in Group IRH-C, respectively). Entire dogs also appeared subjectively overrepresented; however, there was no clear sex predilection.

Azotaemia was relatively uncommon in our population at the time of diagnosis, which also mirrors the previous literature (Stone *et al.* 1983, Mishina *et al.* 1997, Berent *et al.* 2013, Di Cicco *et al.* 2013, Adelman *et al.* 2017). Unlike in previous reports where anaemia has been reported in up to 50% of patients (Stone *et al.* 1983, Holt *et al.* 1987, Di Cicco *et al.* 2013, Berent & Weisse 2014), anaemia was relatively uncommon in this study, occurring in only eight of 41 (20%) dogs at initial presentation [four of 14 (29%) of those in Group IRH-C], and generally mild to moderate in severity. The factors underlying these differences are not clear but may include a lesser severity of disease or duration of haemorrhage, different underlying aetiologies, individual differences in regenerative capacity or potentially overestimation of this complication in previous small case series. Nonetheless, despite the lower incidence and severity of anaemia, the presence of concurrent hypochromia and microcytosis in two dogs with non-regeneration, albeit without serum iron quantification, supports previous suggestions that iron-deficiency may occur as a consequence of chronic renal haemorrhage (Stone *et al.* 1983, Holt *et al.* 1987, Hawthorne *et al.* 1998, Berent & Weisse 2014).

Proteinuria was a common abnormality, occurring in the majority of dogs. Although this abnormality is often attributed to blood-derived proteins and consequently disregarded in haematuric patients, previous studies have suggested that UPC is minimally affected by microscopic haematuria and, although it may be increased by gross haematuria, the impact of this is poorly defined and often overestimated (Vaden *et al.* 2004, Jillings *et al.* 2019). In this study, it is interesting to note that the magnitude of proteinuria was highly variable, with UPCs ranging from 0.2 to 17, and subjectively not obviously related to the severity of haematuria. Although the contribution of blood-derived proteins is difficult to quantify and likely to have impacted on these results, the possibility of other contributing factors, such as glomerular protein loss, cannot be excluded. In humans, glomerular aetiologies of haematuria (*e.g.* IgA nephropathy, Alport syndrome, and thin basement membrane disease) are common and may be distinguished by evaluation of urinary erythrocyte morphology, urine albumin:creatinine ratio and histopathology (Birch *et al.* 1983, Tapp *et al.* 1986, Ohisa *et al.* 2007, Kelly *et al.* 2009, Yuste *et al.* 2015, Bolenz *et al.* 2018). In dogs, however, given the difficulties in interpreting proteinuria in cases with gross haematuria, and that erythrocyte morphology and renal histopathology are infrequently evaluated, differentiation between glomerular

and non-glomerular aetiologies of renal haematuria is challenging. Evaluation of electrophoretic urine protein banding patterns have been shown to be useful for the detection of glomerular and tubulointerstitial damage in dogs with proteinuric chronic kidney disease; however, haematuria may confound interpretation and its use in IRH therefore requires further investigation (Hokamp *et al*. 2018).

Diagnostic imaging findings such as pyelectasia and echogenic urinary bladder sediment were relatively common findings, as also reported in previous canine cases (Stone *et al*. 1983, Holt *et al*. 1987, Berent *et al*. 2013). In addition, ureteral and bladder blood clots were documented in several cases which, despite the low incidence of azotaemia in this population, highlights a potential risk of urinary tract obstruction in patients with IRH. Cystoscopic findings were also similar to those previously described with bilateral haemorrhage occurring at a similar frequency in this study (three of 14 cases) to that previously reported (cumulatively 21% of cases), and highlighting the importance of renal-sparing treatments (Stone *et al*. 1983; Holt *et al*. 1987; Hawthorne *et al*. 1998; Berent & Weisse 2014). However, whereas previous reports have described the left kidney as being predominantly affected, no obvious predisposition was apparent in this study (Stone *et al*. 1983, Hitt *et al*. 1985, Holt *et al*. 1987, Jennings *et al*. 1992, Mishina *et al*. 1997, Hawthorne *et al*. 1998, Berent *et al*. 2013).

Overall, responses following ACEi/ARB treatment compared favourably to a previous study evaluating sclerotherapy with povidone iodine and silver nitrate for IRH which documented complete and partial responses in four of six (67%) and two of six (33%) dogs, respectively (Berent *et al*. 2013). In the current study population, complete resolution of haematuria was documented eight of 19 (42%) dogs, with partial improvement in a further five of 19 (26%). Although it could be argued that this may reflect the inclusion of cases with other aetiologies in Group IRH-S, complete and partial improvements were also documented in a similar proportion of cases in Group IRH-C (43 and 29%, respectively). Furthermore, few dogs were subsequently represented for haematuria and recurrence rates were similar regardless of whether the whole study population or only Group IRH-C are evaluated (21 and 14%, respectively). Although meaningful statistical comparisons were precluded by the small number of cases in the present study and a cause-and-effect relationship cannot be established from this preliminary data, the complete resolution of haematuria in 42% of ACEi/ARB-treated cases suggests that these medical therapies are deserving of further investigation. Nonetheless, it should be noted that, whilst neither had resolution of haematuria, one (Group IRH-S) of the two untreated cases with ascertainable outcome was reported to have had partial improvement. Although this may be attributed to the subjective assessment of gross haematuria, or incorrect diagnosis, it is possible that spontaneous improvement of IRH may also occur and this eventuality should consequently be considered in any future studies evaluating treatment response.

Perhaps contrary to perceived opinion, the prognosis for dogs in our study was generally excellent with median survival times exceeding 1400 days, regardless of the severity of initial presenting signs, institution of ACEi/ARB therapy, or response to treatment. The cause of death or euthanasia was usually not recorded, therefore all-cause mortality (rather than mortality associated with IRH) was reported in the present study, which is likely to be affected by other factors. In support of this, many patients were still alive at the study end-point and, of those that were euthanased, motivations mostly pertained to unrelated conditions or poor quality of life relating to old age. The finding that many dogs, including cases with persistent haematuria (often documented on numerous occasions during follow-up), survived or were still alive several years after diagnosis was an unexpected finding and presumably indicates either that the condition has a waxing/waning or milder course in some dogs, or that their owners learn to tolerate the haematuria once underlying life-threatening or serious pathologies have been ruled out. Nonetheless, one dog was euthanased due to persistent haematuria and hypochromic anaemia, and poor response to treatment, serving as a reminder that IRH may still be associated with severe and life-limiting clinical signs.

This study has several important limitations. Firstly, despite aiming to maximise case numbers by inclusion of dogs from four referral centres and sub-populations with both confirmed and suspected IRH, this study remains limited by the rarity of the disease. Furthermore, despite thorough collation of all available medical records and contacting referring veterinary practices, follow-up information was unavailable or incomplete for a large number of cases. Consequently, the lack of statistical power of the study precluded further statistical analysis of the association between treatment and response, or patient characteristics and clinical parameters that were associated with outcome.

Secondly, inherent to its retrospective nature, diagnostic investigations and treatment decisions were not standardised and clinical data was not always available for review, especially in historic cases. Consequently, complete data could not be obtained in all cases, particularly regarding blood pressure and coagulation assessment, and motivations for euthanasia. Although diagnostic imaging including abdominal ultrasound was performed in all cases, radiography was only performed adjunctively in 25 dogs and small radiopaque uroliths, despite being considered unlikely, could have gone undetected. In addition, given that medical record searches were performed independently in each institution and search terms and methods were not standardised, the possibility of selection bias cannot be excluded. Furthermore, untreated cases tended to be older (2001 to 2016) than those treated with ACEi/ARBs (2012 to 2018) and some dogs also received other treatments in addition to ACEi or ARBs which, although generally considered unlikely, may have had a confounding effect on outcome. Conversely, other medical treatments which have been anecdotally suggested to be beneficial in IRH, such as aminocaproic acid or the Chinese herbal remedy, Yunnan Baiyao, were not administered to dogs in this study. Tranexamic acid, an antifibrinolytic agent, was coadministered with ACEi in two cases; however, haematuria resolved in neither dog. In addition, the timing and extent of follow-up monitoring were variable; many cases had only one follow-up urinalysis performed and, despite the low representation rate, it is therefore possible that any improvement

may have been transient. The duration of haematuria may also have been influenced by the gradual breakdown of blood clots; however, repeat imaging was infrequently performed. Consequently, larger randomised, blinded, placebo-controlled prospective studies would be required to evaluate the efficacy of ACEi/ARB for the treatment of IRH. In addition, additional studies are indicated to clarify the pathogenesis of canine IRH and determine if, and at what frequency, glomerular and non-glomerular aetiologies occur in this species.

Finally, despite the similarities in patient characteristics, diagnostic abnormalities and outcomes between IRH-C and IRH-S sub-populations, our decision to include dogs without confirmed renal haemorrhage (group IRH-S) may have inadvertently led to the inclusion of other aetiologies. For example, a recent case series suggests that macroscopic haematuria without signs of lower urinary tract disease may rarely occur due to lower urinary tract lesions which may not be apparent without cystourethroscopic examination (Himelman *et al*. 2019). However, diagnostic investigation in clinical practice is often influenced by financial factors and client motivations, and the availability and clinical experience of cystoscopy. Applying rigorous inclusion criteria would therefore likely to have resulted in a very small study population and risked exclusion of valuable data, such as that from historic cases and male patients which may have been less likely to have undergone cystoscopy. Consequently, we considered the inclusion of a larger dataset to be valuable in characterising this rare condition but evaluated and presented data from group IRH-C separately in an attempt to mitigate any limitations relating to case inclusion. Similarly, due to the subjectivity associated with evaluating change in gross haematuria, cases with partial improvement (*i.e*. those with reduction in the severity of gross haematuria but persistence of microscopic haematuria) were evaluated separately to those with complete remission or no improvement.

In conclusion, in both Group IRH-C and Group IRH-S in this study, dogs with IRH generally had long survival times and excellent prognoses, irrespective of treatment with ACEi or ARBs, or progression of haematuria. Although complications such as anaemia and euthanasia relating to intractable clinical signs occurred in a small proportion of cases, these outcomes were infrequent in this study population. Improvement or resolution of clinical signs occurred in many ACEi/ARB treated dogs but also occurred in untreated cases. Further studies are therefore required to evaluate the relationship between treatment and outcome, and to elucidate the pathogenesis of canine IRH.

Conflict of interest

None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

References

Adelman, L. B., Bartges, J. & Whittemore, J. C. (2017) Povidone iodine sclerotherapy for treatment of idiopathic renal hematuria in two dogs. *Journal of the American Veterinary Medical Association* **250**, 205-210. https://doi.org/10.2460/javma.250.2.205

Araki, M., Uehara, S., Sasaki, K., *et al*. (2012) Ureteroscopic management of chronic unilateral hematuria: a single-center experience over 22 years. *PloS One* **7**, e36729. https://doi.org/10.1371/journal.pone.0036729

Bagley, D. H. & Allen, J. (1990) Flexible ureteropyeloscopy in the diagnosis of benign essential hematuria. *J Urol* **143**, 549-553.

Bądzyńska, B., Grzelec-Mojzesowicz, M., Dobrowolski, L., *et al*. (2002) Differential effect of angiotensin II on blood circulation in the renal medulla and cortex of anaesthetised rats. *Journal of Physiology* **538**, 159-166. https://doi.org/10.1113/jphysiol.2001.012921

Berent, A. & Weisse, C. (2014) Idiopathic renal hematuria/benign essential renal hematuria. In: Small Animal Soft Tissue Surgery. John Wiley & Sons, Ltd, Chichester, UK. pp 615-622. https://doi.org/10.1002/9781118997505.ch59

Berent, A. C., Weisse, C. W., Branter, E., *et al*. (2013) Endoscopic-guided sclerotherapy for renal-sparing treatment of idiopathic renal hematuria in dogs: 6 cases (2010-2012). *Journal of the American Veterinary Medical Association* **242**, 1556-1563. https://doi.org/10.2460/javma.242.11.1556

Birch, D. F., Fairley, K. F., Whitworth, J. A., *et al*. (1983) Urinary erythrocyte morphology in the diagnosis of glomerular hematuria. *Clinical Nephrology* **20**, 78-84

Bolenz, C., Schröppel, B., Eisenhardt, A., *et al*. (2018) The investigation of hematuria. *Deutsches Arzteblatt International* **115**, 801-807. https://doi.org/10.3238/arztebl.2018.0801

Borchhardt, K., Haas, M., Yilmaz, N., *et al*. (1997) Low dose angiotensin converting enzyme inhibition and glomerular permselectivity in renal transplant recipients. *Kidney International* **52**, 1622-1625. https://doi.org/10.1038/ki.1997.494

Brown, S., Elliott, J., Francey, T., *et al*. (2013) Consensus recommendations for standard therapy of glomerular disease in dogs. *Journal of Veterinary Internal Medicine* **27**, S27-S43. https://doi.org/10.1111/jvim.12230

Chester, A. C., Diamond, L. H., Argy, W. P. Jr., *et al*. (1978) Unilateral primary hematuria. *JAMA: The Journal of the American Medical Association* **240**, 2759. https://doi.org/10.1001/jama.1978.03290250063034

Chou, S. Y., Faubert, P. F. & Porush, J. G. (1986) Contribution of angiotensin to the control of medullary hemodynamics. *Federation Proceedings* **45**, 1438-1443

Cupples, W. A., Sakai, T. & Marsh, D. J. (1988) Angiotensin II and prostaglandins in control of vasa recta blood flow. *The American Journal of Physiology* **254**(3 Pt 2), F417-F424. https://doi.org/10.1152/ajprenal.1988.254.3.F417

Di Cicco, M. F., Fetzer, T., Secoura, P. L., *et al*. (2013) Management of bilateral idiopathic renal hematuria in a dog with silver nitrate. *The Canadian Veterinary Journal* **54**, 761-764

Dooley, R. E. & Pietrow, P. K. (2004) Ureteroscopy for benign hematuria. *Urologic Clinics of North America* **31**, 137-143. https://doi.org/10.1016/S0094-0143(03)00098-3

Fairley, K. F. & Birch, D. F. (1982) Hematuria: a simple method for identifying glomerular bleeding. *Kidney International* **21**, 105-108. https://doi.org/10.1038/ki.1982.16

Goel, S., Mandhani, A., Srivastava, A., *et al*. (2004) Is povidone iodine an alternative to silver nitrate for renal pelvic instillation sclerotherapy in chyluria? *BJU International* **94**, 1082-1085. https://doi.org/10.1111/j.1464-410X.2004.05108.x

Grauer, G. F., Greco, D. S., Getzy, D. M., *et al*. (2000) Effects of enalapril versus placebo as a treatment for canine idiopathic glomerulonephritis. *Journal of Veterinary Internal Medicine* **14**, 526-533. https://doi.org/10.1892/0891-6640(2000)014<0526:eoevpa>2.3.co;2

Hawthorne, J., DeHaan, J., Goring, R. L., *et al*. (1998) Recurrent urethral obstruction secondary to idiopathic renal hematuria in a puppy. *Journal of the American Animal Hospital Association* **34**, 511-514. https://doi.org/10.5326/15473317-34-6-511

Hebert, L. A., Betts, J. A., Sedmak, D. D., *et al*. (1996) Loin pain-hematuria syndrome associated with thin glomerular basement membrane disease and hemorrhage into renal tubules. *Kidney International* **49**, 168-173. https://doi.org/10.1038/ki.1996.23

Himelman, J. F., Berent, A. C., Weisse, C. W., *et al*. (2019) Use of cystoscopy or cystourethroscopy in treating benign macroscopic hematuria caused by lower urinary tract hemorrhage in three dogs. *Journal of the American Veterinary Medical Association* **255**, 90-97. https://doi.org/10.2460/javma.255.1.90

Hitt, M. E., Straw, R. C., Lattimer, J. C., *et al*. (1985) Idiopathic hematuria of unilateral renal origin in a dog. *Journal of the American Veterinary Medical Association* **187**, 1371-1373

Hokamp, J. A., Leidy, S. A., Gaynanova, I., *et al*. (2018) Correlation of electrophoretic urine protein banding patterns with severity of renal damage in dogs with proteinuric chronic kidney disease. *Veterinary Clinical Pathology* **47**, 425-434. https://doi.org/10.1111/vcp.12648

Holt, P. E., Lucke, V. M. & Pearson, H. (1987) Idiopathic renal haemorrhage in the dog. *Journal of Small Animal Practice* **28**, 253-263. https://doi.org/10.1111/j.1748-5827.1987.tb03880.x

Jennings, P. B., Mathey, W. S., Okerberg, C. V., *et al*. (1992) Idiopathic renal hematuria in a military working dog. *Military Medicine* **157**, 561-564

Jillings, E., Squires, R. A., Azarpeykan, S., *et al*. (2019) Does blood contamination of urine compromise interpretation of the urine protein to creatinine ratio in dogs? *New Zealand Veterinary Journal* **67**, 74-78. https://doi.org/10.1080/00480169.2018.1556129

Kashtan, C. E., Ding, J., Gregory, M., *et al*. (2013) Clinical practice recommendations for the treatment of Alport syndrome: a statement of the Alport syndrome research collaborative. *Pediatric Nephrology* **28**, 5-11. https://doi.org/10.1007/s00467-012-2138-4

Kelly, J. D., Fawcett, D. P. & Goldberg, L. C. (2009) Assessment and management of non-visible haematuria in primary care. *BMJ (Clinical research ed.)* **338**, a3021. https://doi.org/10.1136/bmj.a3021

Kupor, L. R., Mullins, J. D. & McPhaul, J. J. (1975) Immunopathologic findings in idiopathic renal hematuria. *Archives of Internal Medicine* **135**, 1204-1211. https://doi.org/10.1001/archinte.1975.00330090076008

Mishina, M., Watanabe, T., Yugeta, N., *et al*. (1997) Idiopathic renal hematuria in a dog; the usefulness of a method of partial occlusion of the renal artery. *Journal of Veterinary Medical Science* **59**, 293-295. https://doi.org/10.1292/jvms.59.293

Ohisa, N., Kanemitsu, K., Matsuki, R., *et al*. (2007) Evaluation of hematuria using the urinary albumin-to-total-protein ratio to differentiate glomerular and nonglomerular bleeding. *Clinical and Experimental Nephrology* **11**, 61-65. https://doi.org/10.1007/s10157-006-0451-6

Rowbotham, C. & Anson, K. M. (2002) Benign lateralizing haematuria: the impact of upper tract endoscopy. *BJU International* **88**, 841-849. https://doi.org/10.1046/j.1464-4096.2001.01228.x

Sangalli, F., Carrara, F., Gaspari, F., *et al*. (2011) Effect of ACE inhibition on glomerular permselectivity and tubular albumin concentration in the renal ablation model. *American Journal of Physiology-Renal Physiology* **300**, F1291-F1300. https://doi.org/10.1152/ajprenal.00656.2010

Stone, E. A., DeNovo, R. C. & Rawlings, C. A. (1983) Massive hematuria of nontraumatic renal origin in dogs. *Journal of the American Veterinary Medical Association* **183**, 868-871

Tanimoto, R., Kumon, H. & Bagley, D. H. (2017) Development of endoscopic diagnosis and treatment for chronic unilateral hematuria: 35 years experience. *Journal of Endourology* **31**(S1), S76-S80. https://doi.org/10.1089/end.2016.0747

Tapp, D. C., Whitaker, W. R. & Copley, J. B. (1986) Primary renal hematuria presenting as unilateral gross hematuria. *American Journal of Nephrology* **6**, 217-219. https://doi.org/10.1159/000167127

Tawfiek, E. R. & Bagley, D. H. (1998) Ureteroscopic evaluation and treatment of chronic unilateral hematuria. *The Journal of Urology* **160**(3 Pt 1), 700-702. https://doi.org/10.1097/00005392-199809010-00018

Tojo, A., Onozato, M. L., Asaba, K., *et al*. (2006) Spironolactone with ACE inhibitor is effective in gross hematuria caused by nephroptosis. *International Journal of Urology* **13**, 990-992. https://doi.org/10.1111/j.1442-2042.2006.01454.x

Vaden, S. L., Pressler, B. M., Lappin, M. R., *et al*. (2004) Effects of urinary tract inflammation and sample blood contamination on urine albumin and total protein concentrations in canine urine samples. *Veterinary clinical pathology* **33**, 14-19

Yuste, C., Gutierrez, E., Sevillano, A. M., *et al*. (2015) Pathogenesis of glomerular haematuria. *World Journal of Nephrology* **4**, 185-195. https://doi.org/10.5527/wjn.v4.i2.185

Supporting Information

The following supporting information is available for this article:

Table S1. Treatments administered prior to referral following the onset of haematuria in the overall study population and in subgroups IRH-C and IRH-S.

Table S2. Additional biochemical abnormalities documented in the overall study population and in subgroups IRH-C and IRH-S at the time of diagnosis.

Table S3. Additional treatments administered in the overall study population and in subgroups IRH-C and IRH-S at the time of diagnosis.