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Outcomes and long-term follow-up of 106 cats treated with subcutaneous ureteral bypass for ureteral obstruction

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Abstract

Background: The implantation of subcutaneous ureteral bypasses (SUB) is the main therapy for cats with benign ureteral obstructions (UO). However, variables associated with outcome and disease progression remain to be characterized.

Hypothesis/Objectives: To describe clinical course, outcome, and rate of progression of cats treated with SUB devices; and to determine variables associated with outcome.

Animals: 106 cats with UO treated with SUB (140 kidneys).

Methods: Retrospective review of the medical records of all cats treated with SUB (2014-2020). Short-term outcome was defined as hospital discharge, and long-term outcome as the rate of progression of serum creatinine >120 days after surgery.

Results: Hospital discharge rate was 86% (91/106). During follow-up, 23 cats (22%) required a revision surgery and 29 cats (27%) had at least one positive urine culture. Median survival time was 1.9 years (95% confidence interval, 1.4-3.2), with urinary-related causes of death in 31/62 cats (50%). Of the clinical variables available at presentation, only younger age was associated with better short-term outcome (P=.008). A lower creatinine at discharge was associated with favorable long-term outcome (P=.02). The median increase in serum creatinine during follow-up was 0.14 mg/dL/year (interquartile range, -0.05 to 0.83) and 75% of the cats were classified as stable. A positive urine culture at the time of diagnosis or treatment with hemodialysis before surgery for severe azotemia were not associated with outcome.

Conclusions and clinical importance: Positive urine culture or severe azotemia at presentation do not predict a worse outcome in cats with UO.

Keywords

Kidney diseases, urinary tract, SUB, hemodialysis.

Abbreviations

HD, Hemodialysis; IQR, Interquartile Range; LT, Long-term; MT, Medium-term; ST, Short-term; SUB, Subcutaneous Ureteral Bypass; Tetra-EDTA, Tetrasodium EDTA; UO, Ureteral Obstruction

Introduction

Feline ureteral obstruction (UO) is a challenging condition associated with high morbidity and mortality.[1,2] In recent years, increased awareness and availability of high-quality imaging have improved its recognition as one of the leading causes of acute kidney injury in cats.[3–8] The migration of calcium oxalate nephroliths into the ureter is the most common cause of obstruction, while other intraluminal (different stone types, blood clots, cellular debris) or extraluminal obstructions (strictures, circumcaval ureters, neoplasia, iatrogenic ligation) are occasionally diagnosed.[1–3,5,8] At presentation, many cats are critically ill, particularly with concurrent dysfunction of the contralateral kidney.[8] Initial medical management primarily aims at treating pain, and restoring fluid, electrolyte and acid-base balance.[8] Animals with severe and persistent hyperkalemia, life-threatening volume overload, or markedly impaired clinical condition may benefit from extracorporeal blood purification with hemodialysis (HD) or from temporary urinary diversion with percutaneous nephrostomy tubes.[8–10] Medical management however only succeeds at relieving the obstruction in 8-17% of the cats.[1,9,11] Therefore, surgery is typically needed early to relieve pressure-related kidney damage and to lessen the risk of progression to end-stage chronic kidney disease.[1,8,9,11,12]

Traditional ureteral surgery (ureterotomy, ureteral resection and anastomosis, ureteroneocystotomy, ureteronephrectomy) leads to frequent complications, including leakage and persistent obstruction due to edema, recurrence of obstructive calculi or stricture at the surgical site.[1,11,13] Mortality rates of 18-39% have been reported.[5,9] Aside from renal transplantation, interventional procedures have emerged with more widely available options. Ureteral stenting is however associated with frequent complications, including re-obstruction, stent migration, encrustation, ureteritis, infections, and urinary tract irritation.[3,5,9,13,14] The implantation of specially designed subcutaneous ureteral bypasses (SUB) composed of a locking loop nephrostomy catheter and a cystostomy catheter linked via a subcutaneous port has been more successful. With shorter surgeries, lower perioperative mortality, less frequent lower urinary tract manifestation and device occlusion, they have evolved to the main therapy of benign UO in cats.[1] Two retrospective studies cumulating 215 cats treated with SUBs reported a hospital discharge rate of 94%[14,15] and other studies have reported outcome and treatment complications.[1–3,5,12,16–19] However, few data are available concerning predictors of short- or long-term outcome or the use of stabilization with HD before surgery.

The primary aims of this study were therefore to describe the clinical course and the long-term follow-up of a large group of cats treated with SUBs, and to identify signalment, clinical, and treatment variables potentially associated with short-, medium-, and long-term outcome. We hypothesized that the success of the treatment with SUB devices is independent of the degree of renal impairment at presentation, and that it results in a stable long-term kidney function in most cats.

Material and Methods

Case selection and clinical data

All cats diagnosed with UO and treated with SUB devices at the Vetsuisse Faculty of Bern between 2014 and 2020 were included in the study and their medical records reviewed. Following data were recorded: signalment, medical history, clinical and laboratory data at admission, diagnostic imaging, surgical and anesthesia reports, clinical and laboratory data from follow-up visits, short- and long-term complications, and cause and date of death. Owners and referring veterinarians were contacted for missing follow-up information.

Routine laboratory evaluation at presentation included CBC, serum biochemistry profile, urinalysis, and urine culture. The serum creatinine concentrations were analyzed further for 3 different periods: hospitalization (presentation, peak, surgery, discharge), early recovery (from discharge to the second flush of the SUB at d120), and long-term progression (from d120 to the last available follow-up). Urine sampling was performed via cystocentesis (prior to SUB placement) or by sterile collection through the SUB port.

Records of abdominal radiographs were reviewed for the presence of radiopaque uroliths. The diagnosis of UO was based on abdominal ultrasound or computed tomography performed by board-certified radiologists or residents. It was confirmed with an antegrade pyelogram performed under fluoroscopy during surgery. Kidney size was categorized as small (length <3.2 cm), normal (3.2-4.4 cm) or enlarged (>4.4 cm).[20] Renal pelves and ureters were considered dilated if their width was >1.6 mm[21] or >1.8 mm[20], respectively, or if reported as such.

Stabilization and SUB device placement

Severely azotemic cats considered clinically unstable for general anesthesia and surgery were treated with HD before SUB placement if the owners agreed to it. Treatments were delivered either with an intermittent HD system (AK200 UltraS, Baxter AG, Glattpark, Switzerland*;* with neonatal circuit and Fresenius FXpaed dialyzer, Fresenius Medical Care, Oberdorf, Switzerland) or with a continuous renal replacement platform (Prismaflex system with Prismaflex HF20 set, Baxter AG, Glattpark, Switzerland), a choice based on availability, cat size, and individual preferences. Treatments were prescribed to correct progressively azotemia, electrolyte and acid-base disorders, as well as fluid imbalances.

General anesthesia for surgery was supervised by a board-certified anesthetist or resident. Surgery was performed by a team of at least one board-certified surgeon or resident and one board-certified internist specialized in nephrology/urology. A SUB device 1.0 or 2.0

(Norfolk Vet Products, Skokie IL) was implanted under fluoroscopic guidance, as described by the manufacturer. The surgeries were classified as uni- or bilateral to describe the number of kidneys undergoing decompressive interventions during one intervention. For bilateral surgeries, two separate SUB systems were implanted. Cats with a negative urine culture were treated with an aminopenicillin/beta-lactamase inhibitor combination for 2 weeks following surgery, and cats with a positive culture for 4 weeks, based on the culture and sensitivity profile.

Complications, outcome, and follow-up

The occurrence of implant obstruction, lower urinary tract signs, urinary tract infections, and other relevant medical conditions diagnosed during follow-up were recorded. Three outcome measures were evaluated to reflect different aspects of recovery and disease progression. Short-term (ST) outcome was defined as survival to discharge from hospital, mirroring the success of the intervention. Medium-term (MT) outcome was defined as the serum creatinine concentration at the second routine recheck (d120), reflecting the stabilization following surgery and the baseline for the long-term management. Long-term (LT) outcome was defined based on the rate of progression of the serum creatinine concentration from d120 to the last follow-up. This rate was calculated as the slope of the regression line of the serum creatinine over time (mg/dL/year) after excluding episodes of hospitalization and fluid therapy. We hypothesized that cats with stable disease would show a normal distribution pattern of their rate of progression, different from cats with a fast progressive disease. Therefore, the study group was separated in cats with stable disease and cats with faster progression by visual examination of the histogram of the rate of progression. A Shapiro-Wilk test of normality was run on the data from cats defined as stable to support the choice of the cutoff. Cause of death was reported for deceased cats and categorized as urinary-related, not urinary-related, or mixed.

Statistical analysis

Original data were organized in Microsoft Excel for Mac (Version 16.52, 2021; Microsoft Corporation, Redmond WA, USA) and data were analyzed with the NCSS 9 Statistical Software Package (2013; NCSS, LLC. Kaysville UT, USA).

Descriptive section: Continuous variables were tested for normality by visual inspection of their histogram and a Shapiro-Wilk test. Because most data were not normally distributed, their descriptive statistics were reported as median (interquartile range, IQR) and they were compared among groups using a Mann-Whitney U test. These variables included age and physical exam, laboratory data at presentation, during hospitalization and during follow-up, duration of anesthesia, surgery and hospitalization, and dialysis-related variables. Laboratory, progression, and outcome data were compared between cats treated with and without HD. Categorical variables were reported as absolute numbers and proportions, and were compared among groups using a chi-square or a Fisher's exact test when the expected counts were <5 in a cell from the contingency tables. They included variables of signalment and outcome compared between cats treated with and without HD. A P-value of .05 was used as cutoff for statistical significance. For multiple comparisons, a Bonferroni correction was performed and the alpha cutoff was altered to .05/k, where k is the number of comparisons on the same dependent variable.

Analytical section: A Kaplan-Meier survival analysis was performed with death of all causes as the event-of-interest. Cats lost to follow-up or still alive at the time of data collection were censored at their last known follow-up. An additional survival analysis was performed by censoring all cats with a clear non-urinary cause of death. A log-rank test was used to compare survival of cats stratified based on the occurrence of urinary tract infections (infected vs non-infected), the use of HD (HD vs nHD), the number of SUBs placed (uni- vs bilateral disease), and the cause of death (urinary vs non-urinary related). The association of selected variables of signalment, laboratory, and treatment with outcome were evaluated using multivariable logistic regression analyses for the categorical outcome variables ST (survived vs died) and LT (stable vs fast progressive), or a multivariable linear regression analysis for the continuous outcome variable MT (creatinine at d120). Gender and age are associated with the risk of urinary tract infections in cats[22] and therefore could affect outcome. Housing with outdoor access affects life expectancy in cats, mostly due to increased risk of non-urinary complications such as trauma, infections, or ingestion of toxicants.[23] Degree of azotemia, evidence of inflammation, presence of urinary tract infection, and uni- vs bilateral obstruction affect disease management and thus potentially the outcome. Treatment with HD indicates a group of cats with severe azotemia that affects disease management and possibly outcome. Following independent variables were therefore assessed for inclusion in the multivariable models by evaluating their statistical associations with the dependent variables: gender (male vs female), age, body weight, housing style (strictly indoor vs outdoor access), creatinine at presentation and discharge, serum amyloid A at presentation, bacteriuria (infected vs not infected) at presentation and overall, treatment with HD before surgery (HD vs nHD), and number of sides (uni- vs bilateral) SUBs were placed at initial surgery or overall. These associations were evaluated with either a linear regression analysis, a chi-square or Fisher exact test, or a Mann-Whitney U test, as appropriate for the type of data. Variables with P-values ≤.1 were included in the multivariable analysis. These variables were added 1-by-1 in the regression model until the addition of further variables did not result in a better-fit model.[24] This was indicated by a lack of a further decrease of the Akaike Information Criterion value in the logistic regression analyses or lack of a further increase in the correlation coefficient R^2 in the linear regression analysis. The following diagnostics were conducted on the obtained logistic regression models: continuous variables were evaluated for linearity by visual evaluation of the plot of their relationship with the logit of outcome; the model fit was assessed using the Pearson chi-square goodness-of-fit statistic and outliers were identified by analyzing the Pearson residuals (<-2 or >2). The percentage of correct predictions and the area under the receiver operating characteristic curve (ROC-AUC) were calculated as additional indicators of model performance. The following assumptions were tested for the linear regression model: linearity of the relationship with the dependent outcome variable by visual evaluation of the scatterplot, normal distribution of the residuals, and absence of collinearity. The strength of the relationship of the model with the dependent outcome variable was evaluated with its R^2-value.

Results

Animals

One hundred six cats of 16 breeds were included in the study. Main breeds were Domestic Shorthair (n=63, 59%), British Shorthair (n=8, 8%), Siamese (n=8, 8%), Persian (n=5, 5%), Maine Coon (n=4, 4%), Birman (n=4, 4%), and Norwegian Forest Cat (n=3, 3%). Other breeds included Bengal and Ragdoll (n=2, 2%), Chartreux, Korat, Ocicat, Oriental Mixed, Selkirk Rex, Siberian and Turkish Angora (n=1, 1%). Age at presentation ranged from 10 months to 16 years, with a median of 7.3 years (IQR, 4.9-9.8). Fifty-four cats (51%) were spayed females, 3 (3%) intact females, 48 (45%) castrated males, and 1 (1%) intact male. Body weight ranged from 1.5-7.5 kg, with a median of 4.2 kg (IQR, 3.5-5.1). The mode of housing was known for 101 cats, with 66 cats held strictly indoor (65%) and 35 cats having uncontrolled outdoor access (35%).

History and clinical data at admission

The most common clinical signs reported by the owners were lethargy (n=86, 81%), anorexia (n=85, 80%), vomiting (n=60, 57%), lower urinary tract signs (n=31, 29%), polyuria-polydipsia (n=22, 21%), and weight loss (n=18, 17%). Additional referral information included the presence of azotemia (n=84, 79%), uroliths detected on abdominal radiographs (n=38, 36%), and ultrasonographic signs suggestive of upper urinary tract obstruction (n=32, 30%) and nephropathy (n=30, 28%).

Median heart rate was 170 beats/min (IQR, 160-200; n=105), respiratory rate 36 breaths/min (IQR, 28-45; n=103), and body temperature 100.4°F (IQR, 99.1-101.5°F; 38.0°C, 37.3-38.6; n=99). Capillary refill time was reported in 94 cats and it was accelerated in 17 (18%), normal in 64 (68%), and prolonged in 13 cats (13%). Abdominal pain was reported in 61 cats (58%) and a heart murmur was audible in 30 cats (28%).

Relevant laboratory results are summarized in Table 1. Bacteriological urine cultures at presentation were available from 77 cats (73%). They were negative in 67 cats and positive in 10 cats, including 5 with *Escherichia coli*, 2 with *Staphylococcus felis*, and one each with *Enterococcus faecalis*, *Enterococcus hirae*, and *Proteus mirabilis*.

Table 1: Main laboratory findings at presentation for 106 cats with ureteral obstruction

Hematology

Variable [reference range]	N	Median [interquartile range]	Values above reference [%]	Values below reference [%]
Hematocrit (%) [27 - 47]	105	30 [25 - 35]	0 [0%]	33 [31%]
WBC ($10^3/\mu L$) [6.5 - 15.4]	94	10.2 [7.2 - 13.8]	20 [21%]	16 [17%]
Segmented neutrophils ($10^3/\mu L$) [2.5 - 12.5]	93	7.9 [5.1 - 11.1]	18 [19%]	1 [1%]
Band neutrophils ($10^3/\mu L$) [0 - 0.3]	93	0 [0 - 0.1]	11 [12%]	-

Biochemistry

Creatinine (mg/dL) [0.6 – 1.6]	106	8.1 [3.7 – 13.4]	101 [95%]	0 [0%]
BUN (mg/dL) [18 – 34]	106	122 [60 – 192]	94 [89%]	2 [2%]
Potassium (mmol/L) [3.7 - 5.3]	106	4.2 [3.7 - 5.2]	25 [24%]	25 [24%]
Sodium (mmol/L) [147 - 157]	106	153 [150 - 155]	13 [12%]	6 [6%]
Phosphorous (mg/dL) [2.5 - 5.9]	106	8.1 [5.3 - 11.8]	72 [68%]	0 [0%]
Total proteins (g/dL) [6.3 – 8.0]	92	7.0 [6.5 – 7.4]	12 [13%]	19 [21%]
Albumin (g/dL) [3.0 – 4.2]	106	3.2 [2.8 – 3.5]	2 [2%]	33 [31%]
Serum amyloid A (µg/mL) [<8.0]	104	6.3 [1.9 - 57.8]	47 [45%]	-
Bicarbonate (mmol/L) [19.7 - 24.8]	63	14.9 [11.9 - 18.8]	1 [2%]	53 [84%]

Urinalysis

Urine specific gravity	64	1.011 [1.009 - 1.016]	
Dipstick: proteins	64	neg + ++ +++ ++++	32 (50%) 16 (25%) 7 (11%) 8 (13%) 1 (2%)
Sediment: red blood cells	64	≤ 5 /hpf 6-10 /hpf 11-20 /hpf >20 /hpf	17 (27%) 5 (8%) 5 (8%) 37 (58%)
Sediment: white blood cells	64	≤ 3 /hpf 4-5 /hpf 6-10 /hpf >10 /hpf	37 (58%) 9 (14%) 7 (11%) 9 (14%)

Abbreviations: BUN, blood urea nitrogen; N, number of cats; hpf, high power field; WBC, white blood cells

Diagnostic imaging findings

Abdominal radiographs were performed in 55 cats. Radiopaque uroliths were identified in 41 cats (75%). Abdominal ultrasound was performed in 105 cats and computed tomography in 1 cat. With these 2 modalities, 211 kidneys from 106 cats were scanned (one cat had only one identifiable kidney). Size measurements were available for 197 kidneys, with 47 kidneys evaluated as small (24%), 85 as normal (43%), and 65 as large (33%). Mineralizations were visible in the pelves or the ureters of 87 cats (82%), 47 unilateral (54%) and 40 bilateral (46%). Mineralizations were observed in the bladder of 24 cats (23%) and in the urethra of 2 cats (2%). An upper urinary tract obstructive pattern with renal pelvic dilation was recorded as unilateral in 44 cats (42%) and bilateral in 62 cats (58%). Ureteral dilation was present in 88 cats (83%), 49 unilateral (56%) and 39 bilateral (44%). Abdominal or retroperitoneal effusion was present in 32 cats (30%).

SUB device placement

One hundred eight surgeries were performed on 140 kidneys, including 76 unilateral (70%), and 32 bilateral (30%). Two cats underwent an additional surgery for the contralateral kidney at a separate presentation. As a result, 72 cats (68%) were carrying a unilateral SUB device and 34 cats (32%) bilateral devices. SUB devices 1.0 were placed in the 65 cats operated prior to May 2018 and devices 2.0 in the 41 cats operated later.

The median duration of surgery was 73 min (IQR, 60-90) for unilateral and 125 min (IQR, 115-180) for bilateral SUBs. Median duration of anesthesia was 150 min (IQR, 123-180) for unilateral and 210 min (IQR, 180-243) for bilateral surgeries. Intra- or perioperative complications were recorded for 16 surgeries (15%) and included device misplacement (n=4), moderate bleeding (n=4), inadvertent opening of the renal capsule (n=3), subcapsular leakage of contrast agent (n=2), capsular leakage (n=1), bladder leakage (n=1), and retained surgical swab (n=1). Minor anesthesia complications were reported in 90 procedures (83%), including hypotension (n=57), hypothermia (n=56), bradycardia (n=31), tachycardia (n=4), other cardiac arrhythmias (n=4), hypoxia (n=4), and others such as pain, tachypnea, hyperthermia, delayed recovery, or early extubation (n=16).

Hospitalization and short-term outcome

Fifteen cats (14%) died or were euthanized during hospitalization, a median of 3 days after surgery (IQR, 2-4). Reasons for death during hospitalization were typically multifactorial. They were considered primarily urinary-related in 3 cats: hyperkalemia from urine leakage, nephrostomy tube misplacement through the renal pelvis, and unsuccessful reconstruction of the urinary tract following spay-related complications. Reasons for death were not directly urinary-related in 7 cats: cardiopulmonary arrest of unexplained cause (n=3), aspiration pneumonia with sepsis (n=2), acute pancreatitis (n=1), and decompensated heart failure (n=1). A combination of urinary (moderate to severe azotemia) and non-urinary complications (pancreatitis, sepsis, heart failure, pulmonary failure, progressive neurological deficits) was reported in 5 cats.

Ninety-one cats (86%) survived to discharge after a median duration of hospitalization of 10 days (IQR, 8-12; range, 5-27). Their median creatinine concentration at discharge was 1.9 mg/dL (IQR, 1.5-2.5; reference range, 0.6-1.6) and their blood urea nitrogen 29.1 mg/dL (IQR, 21.3-43.7; reference range, 18.2-34.2).

Long-term follow-up

Follow-up was available for all cats discharged from hospital, totaling 1653 visits and 196 cat*years, with a median of 1.5 years per cat (IQR, 0.3-3.1). During the first 120 days following discharge, serum creatinine increased by 0.50 mg/dL/year (IQR, -1.51 to +3.11). After that, the progression of the serum creatinine concentration was 0.14 mg/dL/year (IQR, -0.05 to 0.83) until last follow-up or death. The upper limit of the rate of creatinine progression to define stable disease was set as 0.83 mg/dL/year (75 µmol/L/year), based on visual inspection of the histogram of this variable. Fifty cats (75%) with a progression rate ≤0.83 mg/dL/year thus were defined as stable and 17 cats (25%) with a higher rate as fast progressive. The progression rate in the stable cats followed a normal Gaussian distribution with a Shapiro-Wilk test showing no evidence of non-normality (P=.20).

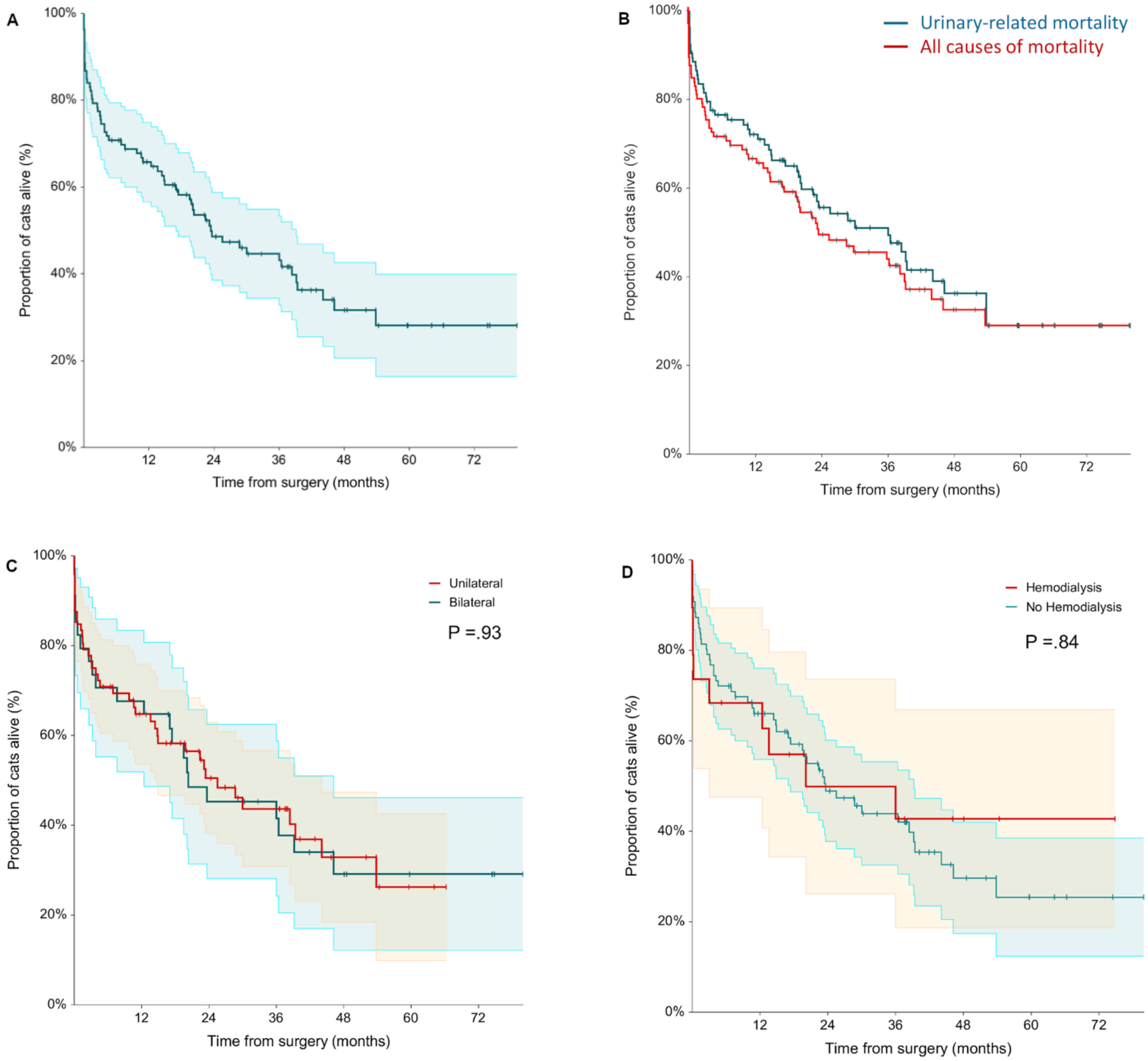
During follow-up, 531 complete urinalyses and 746 urine cultures were performed. Urine specific gravity was 1.017 (IQR, 1.013-1.022). Proteinuria was present in 414 urine samples (78%): 1+ (25-75 mg/dL) in 25%, 2+ (75-150 mg/dL) in 17%, 3+ (150-500 mg/dL) in 22%, and 4+ (>500 mg/dL) in 13% of the samples. Hematuria was reported in 470 urine samples (89%): 5-10 RBC/hpf in 9%, 11-20 RBC/hpf in 9%, and >20 RBC/hpf in 70% of the samples. Leukocyturia was reported in 353 samples (67%): 4-5 WBC/hpf in 13%, 6-10 WBC/hpf in 24% and >10 WBC/hpf in 30% of the samples.

Twenty-nine of the 91 cats that survived to discharge (32%) showed at least one positive culture during the documented follow-up time. For cats that never received tetrasodium-EDTA (tetra-EDTA) injections following the flush of their SUB, the rate of infection was 37% (11/30; 49.3 cat*years of follow-up), for cats treated with tetra-EDTA after some of their flushes 41% (13/32, 106.9 cat*years), and for cats treated with tetra-EDTA following each flush 21% (6/28, 34.2 cat*years). The cumulative incidence of positive cultures for the whole study sample was 9% at presentation, 18% at 6 months, 25% at 1 year, and 27% at 2 years. Only 2 of the 39 cats still alive 2 years after surgery yielded a positive culture after that time if they had never been cultured positive before.

Reported bacteria included *Escherichia coli* (n=18), *Enterococcus faecalis* (n=1), *Enterobacter faecium* (n=1), *Enterobacter cloacae* (n=1), *Mycoplasma sp.* (n=5), *Staphylococcus sp.* (n=3), *Acinetobacter sp.* (n=1), *Actinomyces sp*. (n=1), *Clostridium perfringens* (n=1), *Francisella tularensis* (n=1), *Klebsiella pneumoniae* (n=1), *Proteus mirabilis* (n=1), *Pseudomonas aeruginosa* (n=1), *Streptococcus gallolyticus* (n=1), and *Trueperella sp.* (n=1). Of the 10 cats with a positive culture at the time of surgery, 2 cats cleared the infection (*E. coli*) and remained culture negative for >5 later cultures, 3 cats cleared the infection (*Staphylococcus felis*, *Enterococcus hirae*, *Enterococcus faecalis*) but developed reinfections with other bacteria, 4 cats showed persistence of the initial infection (3 x *E. coli*, 1 x *Staphylococcus felis*) without reinfection, and 1 cat persistence of the initial infection (*Proteus mirabilis*) with reinfections.

During follow-up, 36 cats developed polyuria-polydipsia (40%) and 8 cats were diagnosed with idiopathic hypercalcemia (9%). Fifty-five cats developed lower urinary tract signs (60%), including pollakiuria (n=34), hematuria (n=32), stranguria (n=23), periuria (n=10), dysuria (n=6), urinary incontinence (n=3), and other lower urinary tract signs (n=5). Twenty-three cats (22%) underwent 1 (n=20) or 2 (n=3) revisions of their SUB systems. Six revisions were performed in 5 cats during initial hospitalization. Reasons for these early revisions were intraluminal obstructions (n=4), tube displacement (n=1), and detachment of the nephrostomy tube cuff (n=1). Later revisions were performed a median of 414 days after SUB placement (IQR, 193-568 days). Reasons for these later revisions included intraluminal obstructions (n=12), tube displacement or kinking (n=3), shortening of the intravesicular segment of the cystostomy tubes (n=3), system leakage (n=1), and removal of a nonfunctional obstructed system (n=1).

At the time of data analysis in August 2021, 40 cats were still alive, 62 were deceased (48 were euthanized and 14 died), and 4 were lost to follow-up. The median age at the time of death was 9.2 years (IQR, 3.2-18.1). The cause of death was urinary-related in 31 cats (50%), not urinary-related in 10 cats (16%), and unclear or mixed in 21 cats (34%). The Kaplan-Meier survival analysis yielded a median survival time of 1.9 years (95% CI, 1.4-3.2) for all causes of death (Figure 1A) and 3.0 years (95% CI, 1.8-3.6) when censoring cats with non-urinary causes of death (Figure 1B). Survival time did not differ significantly depending on the number of SUBs placed (P=.93; Figure 1C), the use of HD (P=.84; Figure 1D) or the presence of a urinary tract infection (P=.06; Figure 1E).



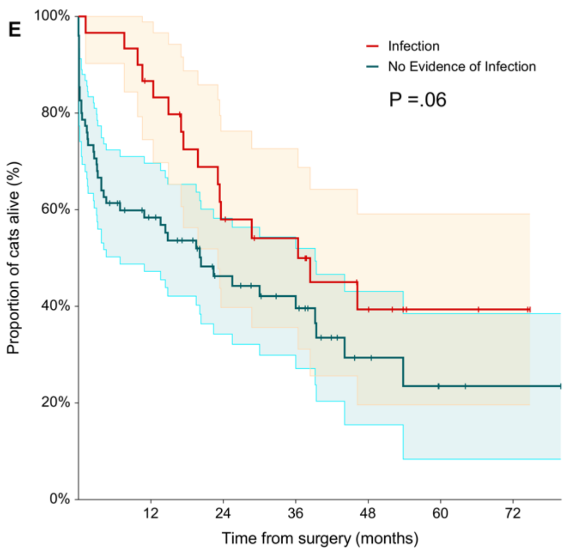


Figure 1: Kaplan-Meier survival curves of 106 cats treated with SUB devices for treatment of benign UO. Cats lost to follow-up or alive at the time of data analysis were censored (+). All cats included in the study (A). Comparison of all causes of mortality with urinary-related causes of death (additionally censoring cats with non-urinary-related causes of death) (B). Comparison of cats with unilateral and bilateral SUB implants (C). Comparison of cats treated with HD and cats treated without HD for stabilization prior to surgery (D). Comparison of cats with all urine cultures negative and cats with at least one positive urine culture (E).

Use of HD for stabilization before surgery

Forty-seven HD treatments were performed in 19 cats (18%) for stabilization before surgery, with a median of 3 treatments per cat (IQR, 2-3). One additional treatment was performed after surgery because of delayed recovery in one of these cats and one additional cat had been treated with HD for a previous episode of UO that resolved without surgery. Treatment specifics are summarized in Table 2.

Table 2: Specifics of the 47 dialysis treatments performed in 19 cats for stabilization before SUB surgery.

	Tx1 (19 cats)	Tx2 (16 cats)	Tx3 or Tx4 (11 cats)
Dialysis platform			
iHD	17	12	10
CRRT	2	4	2
Anticoagulation modality			
RCA	7	4	4
RCA + bolus heparin	12	12	8
Body weight (kg)	4.88 (4.24-6.65)		
Extracorporeal volume (% vascular volume)	19% (13-22)		
Treatment duration (min)	186 (170-220)	252 (240-271)	244 (240-299)
Body weight change (g)	+30 (-33 - +140)	-35 (-128 - +57)	0 (-27 - +67)
Treatment clearance (mL) (mL/kg) (mL/kg/min)	 1500 (1020-2000) 295 (258-309) 1.55 (1.28-1.75)	 3586 (2217-4125) 617 (563-650) 2.33 (2.05-2.72)	 4550 (3825-8350) 1078 (902-1219) 4.22 (2.75-5.38)
CrRR	0.37 (0.32-0.41)	0.57 (0.52-0.60)	0.71 (0.66-0.74)
URR	0.36 (0.34-0.43)	0.59 (0.55-0.61)	0.75 (0.67-0.84)

Abbreviations: CrRR, creatinine reduction ration; CRRT, continuous renal replacement therapy; iHD, intermittent hemodialysis; RCA, regional citrate anticoagulation; URR, urea reduction ratio.
Treatment clearance was calculated as the current dose of treatment administered[25]: volume of blood processed (iHD platform) or volume of therapy fluid corrected for pre-filter dilution (CRRT platform).

Cats treated with HD were more azotemic at presentation (P<.001) than cats treated without, but there was no difference between the groups at the time of surgery (P=.78), discharge (P=.80), and 1 year later (P=0.92, Figure 2). Similarly, survival to discharge (P=.09) and rate of long-term creatinine progression (P=.38) were not different between cats treated with and without HD. However, hospitalization time was significantly longer in cats treated with HD (P<.001).

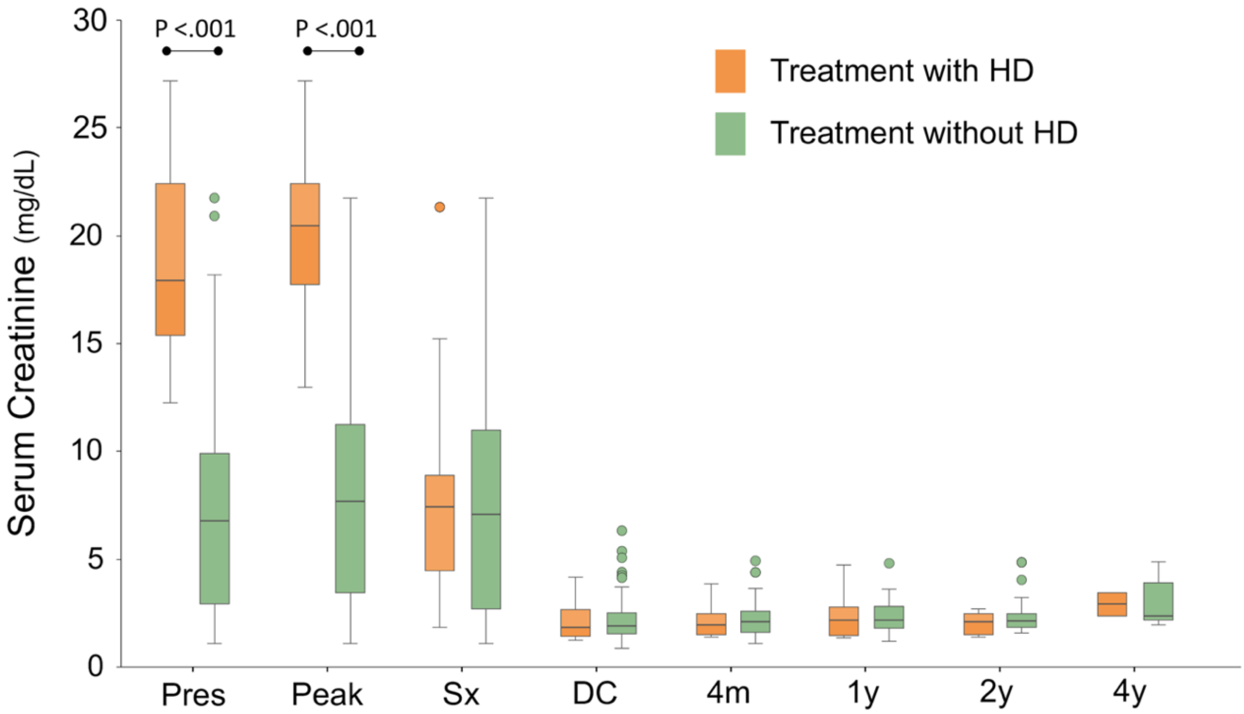


Figure 2: Serum creatinine concentration of 106 cats treated with SUB devices for UO, with comparison between cats treated with hemodialysis (HD, orange) or without hemodialysis (nHD, green) before surgery. Evaluation points included presentation (Pres), peak creatinine during hospitalization (Peak), immediately before surgery (Sx), hospital discharge (DC), 4 months (4m), 1 year (1y), 2 years (2y), and 4 years (4y).

Association of signalment, disease and treatment variables with outcome

When evaluated as univariable statistics (Table 3), younger age, lower body weight, and lower serum creatinine at presentation were associated with better ST outcome. Female gender, younger age, and lower serum creatinine at discharge were associated with better MT outcome. Strictly indoor housing, higher serum amyloid A concentration at presentation, and lower serum creatinine at discharge were associated with better LT outcome. In the multivariable analyses (Table 4), a younger age was strongly associated with better ST outcome and a lower serum creatinine at discharge with favorable MT and LT outcomes.

Table 3: Univariable associations of signalment and laboratory variables with short-, medium-, and long-term outcome in cats with ureteral obstruction treated with subcutaneous ureteral bypass systems.

Variables	P		
ST outcome (discharge from hospital)		Survivors	Non-survivors
Age (y)	.0006[1]	6.9 (4.5 - 9.2)	12.0 (8.2 - 12.5)
Body weight (kg)	.04[1]	4.1 (3.4 - 5.0)	4.5 (3.8 - 6.1)
Creatinine at presentation (mg/dL)	.05[1]	7.8 (3.1 - 13.0)	11.9 (8.5 - 16.8)

MT outcome (creatinine at d120)		More favourable	Less favourable
Gender (F/M)	.10[1]	F: 1.9 (1.5 - 2.4)	M: 2.2 (1.8 - 2.8)
Age (y)	.01[2]	β = 0.059 (95% CI, 0.013 - 0.105) r^2 = 0.08	
Creatinine at discharge (mg/dL)	.0001[2]	β = 0.42 (95% CI, 0.26 - 0.58) r^2 = 0.27	

LT outcome (stable vs fast progression)		Stable	Fast progression
Indoor status (in/out)	.007[3]	in: 35/41 (85%) out: 12/22 (55%)	in: 6/41 (15%) out: 10/22 (45%)
Creatinine at discharge (mg/dL)	.007[1]	1.7 (1.4 - 2.2)	2.3 (1.7 - 3.4)
SAA at presentation (µg/mL)	.02[1]	12.1 (2.2 - 90.8)	3.3 (0.0 - 8.5)

Statistic: Mann-Whitney U test[1]; Linear regression analysis[2]; Fisher exact test[3].

Abbreviations: ST, short-term; MT, medium-term; LT, long-term; SAA, Serum Amyloid A.

Table 4: Results of the multivariable logistic regression analyses (ST and LT) and linear regression analysis (MT) of variables potentially associated with short, medium, and long term outcome in cats with ureteral obstruction treated with SUBs.

ST outcome (discharge from hospital)

Variable	β	SE	OR	95% CI of OR	Wald-P
Intercept	3.25	1.33	25.9	1.90 - 351	.015
Age (y)	-0.24	0.09	0.79	0.66 - 0.94	.008
Body weight (kg)	-0.21	0.27	0.81	0.48 - 1.37	.43
Creatinine at presentation (mg/dL)	-0.02	0.05	0.99	0.90 - 1.08	.75

77.1% cats classified correctly; ROC-AUC, 0.78

Pearson chi-square, 16.1 (P =.0001); 7 outliers on Pearson residual analysis

MT outcome (creatinine at d120)

Variable	β	SE			P
Intercept	1.17	0.21			<.0001
Age (y)	0.032	0.021			.14
Creatinine at discharge (mg/dL)	0.37	0.09			<.0001
Gender (M/F)	0.040	0.153			.79

R^2, 0.29; P <.0001

LT outcome (stable vs fast progression)

Variable	β	SE	OR	95% CI of OR	Wald-P
Intercept	2.70	1.19	14.9	1.44 - 154	.02
Creatinine at discharge (mg/dL)	-1.18	0.52	0.31	0.11 - 0.85	.02
Housing status (indoor/outdoor)	-1.10	0.69	0.33	0.09 - 1.28	.11
SAA at presentation (μg/mL)	0.008	0.008	1.01	0.99 - 1.02	.34

73.8% cats classified correctly; ROC-AUC, 0.80

Pearson chi-square 8.69 (P = .003); 1 outlier on Pearson residual analysis

Discussion

With 106 cats treated with SUB devices for benign UO, findings of this study show that, of the clinical variables routinely available at presentation, only age was associated with outcome. Even cats presented with severe azotemia, and needing initial stabilization with blood purification techniques, did not differ significantly in their outcome compared to cats with lighter degrees of azotemia. Upon long-term follow-up, the kidney function remained stable in 75% of the cats, with a median increase of the serum creatinine of 0.14 mg/dL/year. A cutoff of 0.83 mg/dL/year seemed to separate cats with stable disease from cats with faster progression. These results confirm that SUB devices are a viable option for treatment of benign UO in cats.[5,14,15]

The study sample included cats from a very heterogenous population in terms of breeds, sex, age and housing. This is consistent with a recent study that demonstrated the lack of association between these variables and the development of UO.[26] The higher prevalence of fast progression in cats with uncontrolled outdoor access compared to cats with strict indoor housing most likely reflects the indirect effect of non-urinary complications resulting from this lifestyle rather than a direct effect on the renal function. This is supported further by the lack of significant association between housing style and outcome in the multivariable analysis.

Our study reports a higher rate of intraoperative complications (15%) and a lower rate of hospital discharge (86%) than in major previous studies (7%[14] and 94%[14,15], respectively). This possibly indicates differences in surgical experience with the technique, in surgical and imaging equipment, and in case selection. The median serum creatinine at presentation (8.1mg/dL) was higher than in these studies (5.3mg/dL[15] and 6.6mg/dL[14]). Procedure-related complications occurred mostly in the first half of the study, suggesting a learning curve with the surgical technique and the case management. The retrospective design of the studies and the lack of standardized complication assessment and reporting may contribute further to these differences. Other studies with a small sample size typically report higher rates of complications: 25/81 (31%)[15] and 4/24 (17%).[12] Failure of the SUB systems during LT follow-up led to implant revision in 22% of the cats, which is comparable with recent studies.[3,12,14,15]

The median survival time of the study cats was 694 days (1.9 years), similar to that reported in other major studies: 530[3], 821[15] , and 827 days[14]. Half of the cats were euthanized or died of urinary-related causes. However, with 34% unclear or mixed causes, these data are difficult to compare between studies.

The multivariable analyses of potential predictors of outcome suggest that young cats were more likely to survive to discharge and that a lower creatinine concentration at discharge was correlated with a lower creatinine concentration 120 days after surgery and with a slower LT progression. Variables such as positive urine cultures were not negatively affecting the outcome and almost showed an inverse association. Since a direct protective effect by the bacteria is improbable, prospectively designed studies are necessary to evaluate a possible protective effect of the antimicrobials used to treat these infections. Altogether, the antimicrobial use policy in the study institution can be qualified as restrictive, although a differentiation between subclinical bacteriuria and true urinary tract infection was often not possible clinically. Positive urine cultures were identified in 31 cats (32%) during the whole study. This prevalence is comparable to previous reports (21-36%[2,3,12,14–16,18,19]), however, it is markedly influenced by the duration of the follow-up, as the likelihood of getting at least one positive culture increases with the number of cultures performed on an individual cat.

The rate of infection in the 28 cats treated with tetra-EDTA following each flush was 21%, compared to 39% in the 62 cats never or only partially treated with tetra-EDTA. However, because the cumulative follow-up time in these two groups of cats treated was very different, the true protective effect of this treatment cannot be assessed. Although reported to decrease the risk of mineralization (from 24% to less than 4.5%) during 15 months after surgery[14], the routine use of tetra-EDTA as part of the maintenance protocol is not correlated with the likelihood of a positive culture within 3 months of surgery.[18]

The outcome of cats treated with HD prior to surgery was not different from that of cats treated without, despite more profound azotemia at presentation. This suggests a real benefit in anesthetic safety for these cats with severe metabolic, fluid, electrolyte and acid-base disorders, although the exact criteria to use for treatment decision in these cats remain to be defined. In the meantime, immediate availability of HD or surgery and disease variables indicative of the degree of functional disturbances should be considered.

These findings suggest that a higher creatinine concentration at admission and the need for HD for stabilization prior to surgery should not be viewed as negative prognostic factors. This result contrasts with the higher mortality of cats treated for ureteral calculi[11] but is in accordance with a more recent study where the need for HD was not associated with survival time.[14]

To the authors' knowledge, this is the first numerical analysis of creatinine progression reported in a large group of cats with SUB implants and regular follow-ups over a long time.

The median increase in serum creatinine was 0.14 mg/dL/year, with 25% of the cats classified as fast progressive based on a higher progression rate than the main group of cats. The cutoff of 0.83 mg/dL/year (75 μmol/L/year) was defined by visual examination of the data repartition and should be confirmed in prospective studies. These data suggest a relatively slow and linear progression of azotemia in most cats despite the presence of chronic kidney disease in all of them. The only variable associated with this rate of progression in the multivariable analysis was the serum creatinine concentration at discharge from hospital.

Our study presents several limitations, mostly associated with its retrospective nature. However, the low percentage of cats lost to follow-up, the uniform recheck protocol throughout the study with almost all rechecks performed at the same institution, and the limited number of clinicians involved in the case management, contributed to the quality of the data. Another limitation is the single-center design, possibly causing a systematic bias and limiting the generalizability of the results. However, this may contribute to more standardized and consistent methods, despite minor changes introduced to the procedure and to the case management over time. These includes a gradual improvement of the skills of the clinicians and surgeons, the use of tetra-EDTA injections for the flush procedures, and the transition from the SUB system 1.0 to 2.0.

In conclusion, our results suggest that SUB devices are a feasible option to treat cats with benign ureteral obstruction and that the procedure is associated with a relatively low complication rate, a slow progression of chronic kidney disease, and a long survival time. Cats with severe azotemia at presentation requiring stabilization with blood purification techniques before surgery show similar outcomes as less severely affected cats.

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