Received: 1 February 2019 | Accepted: 15 July 2019

DOI: 10.1111/jvim.15582

STANDARD ARTICLE

Journal of Veterinary Internal Medicine Open Access

ACVIM American College of Veterinary Internal Medicine

Therapeutic use of tetrasodium ethylenediaminetetraacetic acid solution for treatment of subcutaneous ureteral bypass device mineralization in cats

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Abstract

Background: Subcutaneous ureteral bypass (SUB) device placement is an increasingly popular treatment option for decompression of ureteral obstruction in cats. Mineralization occlusion of the device occurs in a minority of cases but is the most common complication.

Objective: To evaluate a 2% tetrasodium ethylenediaminetetraacetic acid (tEDTA) solution for treatment of mineralization occlusion in cats with SUBs.

Animals: Six client-owned cats (8 obstructed devices).

Methods: Case series. Each cat was found to have device occlusion based on a combination of ultrasound examination, SUB irrigation, and failure to identify another cause of device obstruction. Each SUB was drained, irrigated using sterile saline, and infused with 1-2 mL of 2% tEDTA solution. Success was defined as normalization of flow during subsequent ultrasound visualization while irrigating. The volume and frequency of tEDTA instillations, time to achieve device patency, follow-up biochemical and ultrasound findings, and future reobstruction events were recorded.

Results: Resolution of mineralization was documented in all 8 SUBs. Reobstruction events occurred in 2 cats, all of which resolved after additional tEDTA infusions, but 1 cat ultimately required device exchange at 356 days from the first tEDTA infusion. In 1 cat, a single infusion was prematurely discontinued because of persistent pelvic dilatation after 1.25 mL of tEDTA had been instilled. No complications were observed.

Conclusions and Clinical Importance: Tetrasodium EDTA infusions can be safely considered as a treatment option for mineralized SUB devices in cats. This solution was easily infused, well tolerated, and avoided the need for SUB device exchange in the majority of cats in which it was used.

KEYWORDS

kidney, renal calculi, renal/urinary tract, ureteral calculi, ureteral obstruction, ureteral surgery, ureters

Abbreviations: BUN, blood urea nitrogen; CKD, chronic kidney disease; IRIS, International Renal Interest Society; SUB, subcutaneous ureteral bypass device; tEDTA, 2% tetrasodium ethylenediaminetetraacetic acid; UTI, urinary tract infection.

1 | INTRODUCTION

Recent studies evaluating 174 subcutaneous ureteral bypass (SUB) devices in 134 cats with benign ureteral obstructions identified a high success rate of decompression with a very low perioperative mortality rate (6%).[1-6] The most significant complication seen with the SUB device was mineralization occlusion, documented in 24% of devices at a median time of 463 days postoperatively. However, as a result of reestablishment of ureteral patency over time, only 12.7% of the devices had to be exchanged.[1]

Mineralization can occur anywhere throughout the system, but it is most common at the ends of the device within the renal pelvis or urinary bladder lumen. It is believed to occur secondary to calcium oxalate material deposition within the lumen of the device (Figure 1). If the ureter is not patent because of persistent stone or stricture, then mineralization of the SUB device can lead to reocclusion of the renal outflow tract and another obstructive event, resulting in further renal compromise. Substantial effort has been made to identify an irrigating solution that could prevent or treat (or both) mineralization of these devices utilizing a subcutaneous port design.

Ethylenediaminetetraacetic acid (EDTA) is a substituted diamine molecule containing 4 carboxyl groups and occurs as several salts such as disodium EDTA, trisodium EDTA, and tetrasodium EDTA (tEDTA).[7] This molecule has a wide variety of medical uses because of its ability to chelate heavy metals and minerals, particularly those with +2 or +3 valence, and historically has been used as chelation treatment for lead or mercury toxicity with few reported negative systemic adverse effects.[8,9] More recently, EDTA's chelating properties were investigated for improving cardiovascular health in patients with diabetes, as well as for unique antimicrobial and antibiofilm properties in wound and indwelling catheter management.[10-16]

The chelating properties of EDTA also have been explored as an irrigation solution for dissolving calcium-containing nephroliths in human kidneys.[17,18] In over 260 patients evaluated, over 50% had complete dissolution of their stones (146/260 patients).[18] Other studies using various solutions containing EDTA suggested potential topical urothelial toxicity.[18-20] As a result, EDTA irrigation techniques for chemolysis of calcium stones were never adopted. However, more recent studies utilizing lower concentrations of EDTA solutions for irrigation have found no adverse effects on the urothelium.[21]

Since the implementation of routine irrigation of the SUB device using 2% tEDTA, we have observed a decrease in both the infection and mineralization rates associated with SUB devices used in cats. In addition, irrigating with 2% tEDTA appears to clear SUB device occlusions, avoiding the need for device exchange in these cases. Our objective was to report the use of a commercially available locally infused 2% tEDTA solution for the treatment of SUB device mineralization occlusion in a group of cats that presented with poor device flow during irrigation. Our hypothesis was that serial infusions of 2% tEDTA could clear a mineralized SUB device, often avoiding the need for SUB device exchange.

2 | MATERIALS AND METHODS

2.1 | Case selection

Between February 2017 and August 2018, cats that were documented to have SUB device occlusion from suspected mineralization, for which tEDTA infusions were used for demineralization, were serially enrolled in the study. Ultrasonographic imaging was used to determine the presence and extent of renal pelvic dilatation, associated hydroureter, and the presence of mineralized material within the renal pelvis, urinary bladder, or both. In addition, ultrasonography was used to visualize the patency of the SUB device in the renal pelvis and urinary bladder by identifying bubble flow during saline infusion. Radiographs or fluoroscopic images were taken if an obstruction was identified to confirm the device was not kinked or misplaced. A SUB obstruction was diagnosed if there was failure to see bubbles in 1 or

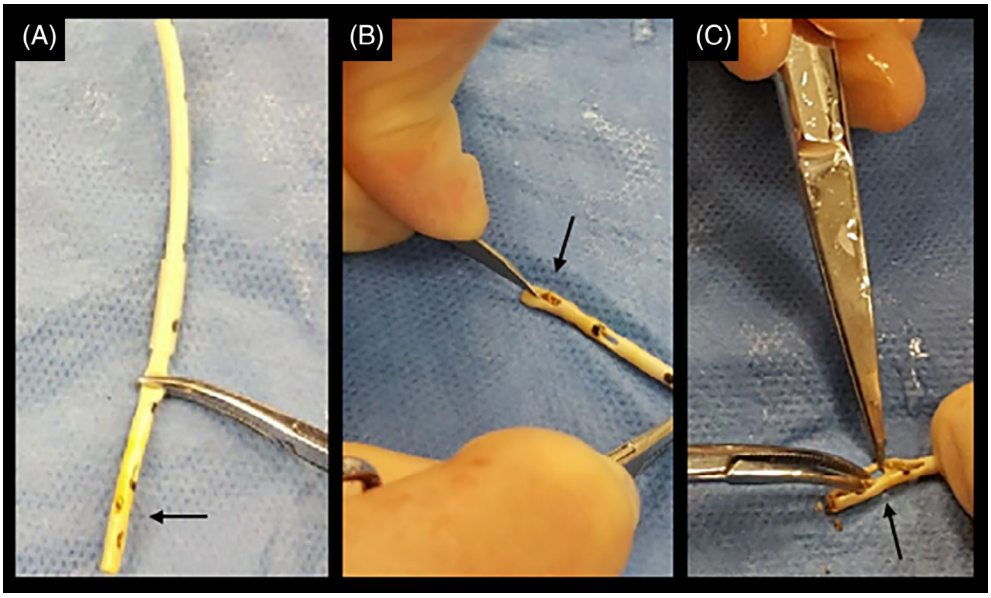

FIGURE 1 Mineralization on SUB device seen during SUB device exchange. A, Yellow mineralization deposits (black arrow) are identified at the end of the cystostomy portion of the SUB catheter below the hemostats. B, Opening of the cystostomy catheter lumen using a #11 blade at mineralization deposits (black arrow). C, Calcium oxalate mineral deposition (black arrow) along with multiple calculi are seen in the lumen of the cystostomy catheter

both sides of the catheter, failure to drain urine from either side despite ultrasound visualization confirming the presence of urine in the renal pelvis or bladder, or documentation of occlusion based on contrast infusion during fluoroscopic visualization. Short-term (0-30 days) and long-term (>30 days) clinical, imaging, and biochemical outcomes were recorded.

2.2 | Historical and laboratory data

Signalment, indication for SUB device placement, history of chronic kidney disease (CKD), history of ionized hypercalcemia, presenting clinical signs, serum biochemical data, microbiological results, and imaging findings were recorded.

2.3 | SUB irrigation procedure

A SUB device irrigation was performed as described in the instruction for use manual (Figure 2).[22] The patient was placed in dorsal recumbency, typically without sedation unless necessary. The skin overlying the SUB port site was clipped of hair and aseptically prepared. With the SUB irrigation kit, a 3-mL empty syringe, a 3-mL syringe filled with sterile saline, and a T-port were attached to a 3-way stopcock. A non-coring 20- or 22-gauge Huber point needle then was connected to the T-port. In a sterile manner, the Huber needle was placed inside the silicone diaphragm and into the well of the SUB port. An ultrasound examination then was performed, measuring the renal pelvis size and evaluating the renal and bladder catheters and the urinary bladder wall. The device was evaluated inside the renal pelvis and urinary bladder for any evidence of mineral shadowing, and if present recorded. The empty syringe then was used to collect a 2-3 mL urine sample that was used for urinalysis and culture when indicated. If samples were to be submitted in a patient with bilateral SUBs, urine from both SUB devices was collected and mixed. Next, sterile saline was firmly injected into the SUB device in 0.3-0.5 mL aliquots while monitoring the renal pelvis to document bubbles and patency. The solution was not agitated before irrigation. After each infusion, an equal volume of fluid was removed from the system with the syringe to avoid overfilling the renal pelvis. Once bubbles were visualized within the renal pelvis and the instilled fluid volume was removed, the urinary bladder was imaged by ultrasonography and another 0.3-0.5 mL irrigation was performed to visualize bubbles in the urinary bladder. The same amount of saline that was injected into the SUB device was again drained. If bubbles were seen in both the renal pelvis and bladder, then the SUB system was deemed patent. In the event that urine could not be drained despite the presence of fluid in the urinary bladder or renal pelvis, bubbles were not easily seen to flow into the urinary bladder or renal pelvis, a minimal quantity of

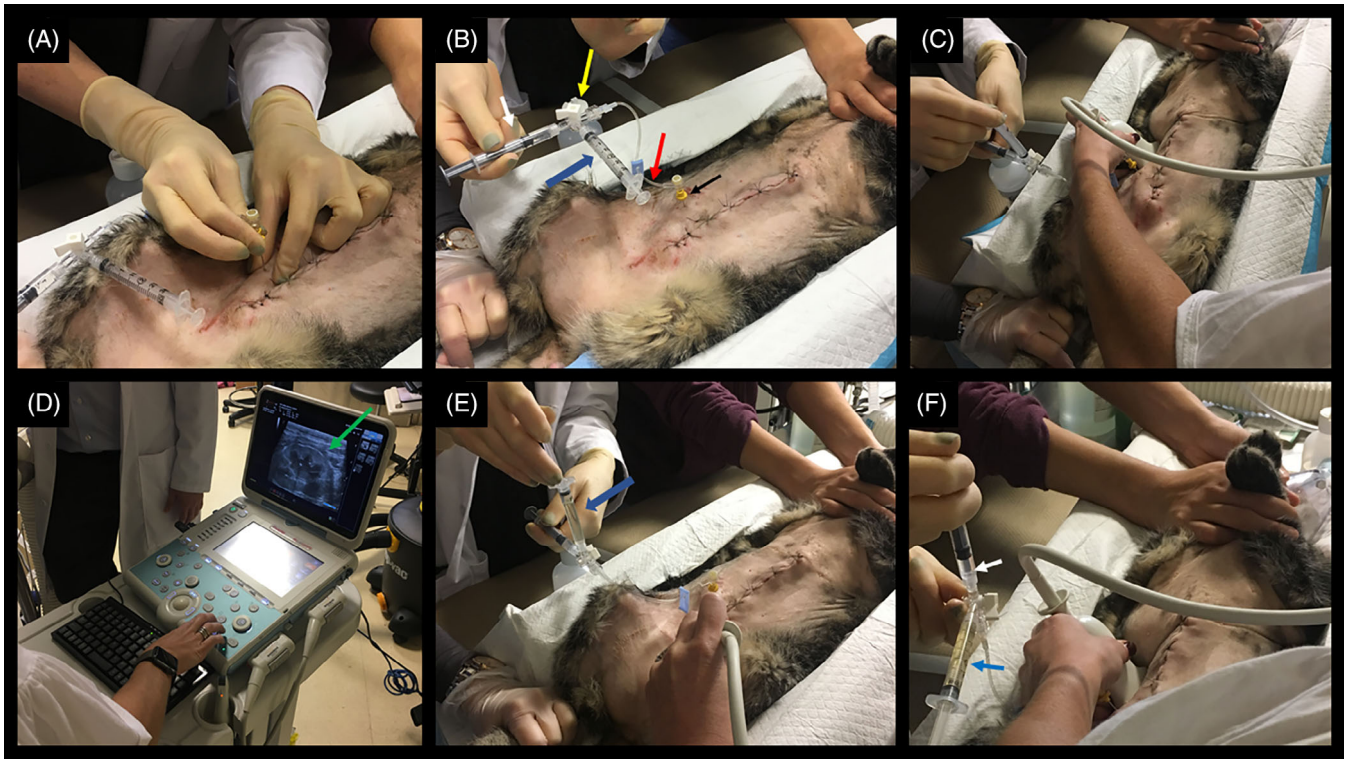

FIGURE 2 Normal SUB irrigation setup and irrigation procedure. The cat is placed in dorsal recumbency and the port site is clipped and aseptically prepared using chlorhexidine surgical scrub. A, The Huber needle is inserted into the port using sterile technique and sterile gloves. Once metal is hit with the needle (black arrow) and the needle is within the well, then the system is in place. B, The 3-mL empty syringe (blue arrow), 3-way stopcock (yellow arrow), T-port (red arrow), 3-mL syringe containing sterile saline (white arrow), and Huber needle (black arrow) in the SUB port. C, Ultrasound is used to evaluate the renal pelvis and urinary bladder, measuring size and evaluating for any pathology. D, Ultrasound image of the kidney with the SUB coming through the caudal pole (green arrow). E, Urine is drained (blue arrow) from the port and submitted for analysis if applicable. F, Saline is infused into the system (white arrow) while monitoring the kidney using ultrasound guidance

bubbles was seen compared to normal, or abnormal resistance was encountered when draining or irrigating, a SUB device occlusion was suspected and a radiograph or fluoroscopic image was taken to ensure that catheter kinks were not present. During fluoroscopic imaging, the cat's rear legs would be pulled forward and backward to ensure a dynamic kink was not visualized. Additionally, contrast infusion into the SUB was attempted to evaluate for device occlusion. If a kink was not identified and no other cause for obstruction was evident, mineralization of the device was presumed. If progressive renal pelvic dilatation was identified during imaging studies, SUB device occlusion was diagnosed and considered to be associated with recurrent renal outflow tract obstruction. If no renal pelvic dilatation was evident despite the device not draining or irrigating normally, then a device occlusion without a concurrent ureteral obstruction was diagnosed. The lack of hydronephrosis in these cats was suspected to be a consequence of a patent native ureter and resolution of the original obstructive lesion (eg, stone, debris).

Once the device was deemed obstructed (no flow into 1 or both catheters) or partially obstructed (decreased flow or drainage into 1 or both catheters), 1-2 mL of tEDTA was slowly infused into the system in 0.3-0.5 mL aliquots, allowing time for the renal pelvis to drain before another aliquot was infused. Care was taken to ensure that progressive renal pelvic dilatation did not occur during ultrasound monitoring of the renal pelvis. If the renal pelvis remained persistently dilated at any point during the infusion, the infusion was stopped and the volume infused was recorded.

2.4 | 2% tEDTA infusion solution

The 2% tEDTA solution is a proprietary combination solution composed of 2% tEDTA (the primary active ingredient for chelation), sodium hydroxide (for pH adjustment), saline (nonactive ingredient), and sterile water. The solution has a pH of 10.2-10.8, has an osmolarity of 285-320 mOsm/L, and is provided in a sterile 12-mL syringe containing 2 mL of solution.

2.5 | Infusion protocol and data collection

Patients presenting with SUB device occlusion secondary to suspected mineralization received a 2% tEDTA irrigation in an attempt to chelate calcium from the mineralized material, leading to dissolution of the mineralized deposit or stone. The schedule for additional tEDTA irrigation followed a general timeline but varied depending on documentation of improvement or progression of clinical findings and variable client compliance. The basic schedule is outlined below:

Day 1: Serum or plasma creatinine, total solids, blood urea nitrogen (BUN), ionized calcium concentrations, PCV, urinalysis, urine microbiological culture, urinary tract ultrasound, and a SUB device irrigation using ultrasound guidance as described above. The saline irrigation was followed by 1-2 mL of 2% tEDTA infusion as described above.

Days 2-5: One to 3 SUB device irrigations with 2% tEDTA infusion. The frequency of irrigations during this period was dependent on improvement in pyelectasia, SUB patency, or both. If improvement in pyelectasia and SUB device patency was noted on ultrasound examination after day 1, 1 to 2 more irrigations with tEDTA were recommended during the next 2 to 5 days. If no improvement in pyelectasia and SUB patency was noted, 2 to 3 more irrigations with tEDTA were recommended during days 2-5. If multiple irrigations were conducted during days 2-5, only 1 irrigation was conducted on each day.

One-week reevaluation: Standard urinary tract ultrasound examination with a single SUB irrigation and 2% tEDTA infusion.

Two-week reevaluation: Standard urinary tract ultrasound examination with a single SUB irrigation and 2% tEDTA infusion.

Four- to 6-week reevaluation: Serum or plasma creatinine and BUN concentrations, urinary tract ultrasound examination with a single SUB irrigation and 2% tEDTA infusion once within this time frame.

Every 3 *months thereafter*: Serum or plasma biochemical assessment, PCV, total solids concentration, urinalysis, urine microbiological culture, urinary tract ultrasound examination with a SUB irrigation and 2% tEDTA infusion.

2.6 | Statistical methods

Because of small sample size, results were evaluated using descriptive statistics only and all data collected in this study was summarized as medians and ranges, but means also are provided.

3 | RESULTS

3.1 | Case selection

Six cats with eight obstructed SUB devices were evaluated between February 2017 and September 2018. Of the 6 cats, 3 (50%) cats had a unilateral SUB device and 3 (50%) had bilateral devices. Two of the 3 cats with bilateral SUBs presented with obstruction of both SUBs. The third cat with bilateral SUBs presented with a unilateral obstruction. Overall, 6 tEDTA infusion protocols for demineralization were performed in 6 cats and 8 devices. Reasons for original SUB device placement in each cat were for treatment of ureteral obstructions secondary to ureterolithiasis (5, 62.5%), stricture (2, 25%), or both (1, 12.5%). The study population consisted of 5 female spayed and 1 male castrated cat. There were 5 domestic short hair and 1 sphynx cat. The median age at the time of presentation for SUB device occlusion was 11.62 years (range, 6.3-15.9; mean, 11.1) and the median weight was 4.17 kg (range, 3.2-4.45; mean, 3.98). The median time the SUB device was indwelling before mineralization obstruction and tEDTA infusion was 504.5 days (range, 118-1021; mean, 490.5).

3.2 | Relevant history, clinical presentation, and imaging findings

One of the 6 cats had a history of ionized hypercalcemia. One cat had a history of recurrent urinary tract infection (UTI; 1/6), but all cats were negative for a UTI at the start of the infusion protocol. Of the 6 cats in this study, 3 had International Renal Interest Society (IRIS) stage II CKD and 3 had IRIS stage III CKD.

One cat (1/8 SUBs) presented with acute, severe illness from ureteral obstruction with tachypnea, progressive pyelectasia, and a 24- to 48-hour history of progressive hyporexia, vomiting, and inappropriate urination.

The other 5 cats (7/8 SUBs) had occlusions initially noted on a routine SUB irrigation. Of these 5 cats (7 SUBs), 3 kidneys had evidence of renal pelvic dilatation, totaling 4 of 8 SUBs overall having some renal pelvic dilatation caused by outflow tract obstruction associated with mineralization. Additionally, 2 of the 5 cats with occlusions noted on routine SUB irrigation had a recent history of nonspecific clinical signs. One cat had a recent history of hyporexia for several days, which resolved with an unknown dose of PO mirtazapine, and 2 episodes of inappropriate urination after household environmental changes. The second cat with nonspecific clinical signs had a new history of inappropriate urination twice in 1 month and 1 episode of inappropriate defecation but was otherwise normal and did not have renal pelvic dilatation on presentation. The remaining 3 cats had no evidence of clinical illness before presentation.

3.3 | SUB irrigation findings

All cats had abnormal SUB irrigations. Based on these abnormal irrigations, the location of SUB occlusion within the SUB device could be identified using ultrasound examination in 7 of 8 SUBs. Of these 7 SUBs, the occlusions were documented in the nephrostomy catheter only (2/7 SUBs), the cystostomy catheter only (2/7 SUBs), and in both the nephrostomy and cystostomy catheters (3/7 SUBs). In the remaining SUB device, the exact location of the occlusion could not be identified because immediately after a difficult aspiration from the SUB, patency was restored with a single irrigation of both the bladder and kidney, which suggested occlusion in the port.

In 4 of the 8 SUBs, urine only could be aspirated with difficulty but the device could be irrigated. Three SUBs were difficult to irrigate, but an SUB irrigation could be performed in small increments and the SUBs became more patent with time, indicating partial obstruction. One SUB was both difficult to aspirate and irrigate and did not improve during the irrigation procedure.

Renal pelvic dilatation was noted in 4 of 8 kidneys with a median diameter on ultrasound examination in a transverse plane of 6.75 (range, 4.5-14; mean, 8) mm. Macroscopic hematuria was observed at initial drainage in 2 of 6 initial urine samples.

3.4 | Clinicopathologic and laboratory data

On presentation, the median serum creatinine concentration was 2.7 (range, 2.3-4.6; mean, 3.1; reference range, 0.8-2.1) mg/dL, BUN concentration was 56.5 (range, 37-164; mean, 71.2; reference range, 17-35) mg/dL, symmetric dimethylarginine concentration (SDMA) was 24.5 (range, 21-61; mean, 33; reference range, 0-14) μg/dL, and ionized calcium was 1.3 (range, 0.9-1.3; mean, 1.2; reference range, 1.1-1.3) mmol/L.

Median urine specific gravity on presentation was 1.018 (range, 1.009-1.024; mean, 1.017) and urine pH was 6.2 (range, 6-7; mean, 6.4). All cats had evidence of microscopic hematuria (reference range, <10 RBC/hpf) and 2 of 6 cats had pyuria (reference range, <10 WBC/hpf). Epithelial cells were visualized in 5 of 6 samples, and no cat had bacteriuria or a positive urine culture.

3.5 | Protocol data

Six demineralization protocols were conducted in 6 cats and 8 SUBs over the course of these treatments. The SUB devices were irrigated during the first week 1-3 times, then once a week for 1-3 weeks, then once a month for 1-6 months, and every 3 months thereafter. This variation in the schedule was based on client convenience, severity of outflow obstruction, and client compliance. The median amount of 2% tEDTA instilled per infusion was 1.5 (range, 1-7; mean, 1.6) mL. After restoration of SUB patency, all cats continued to have their SUBs irrigated routinely with tEDTA on subsequent follow-up visits, resulting in 127 tEDTA infusions being conducted in the 8 SUBs throughout the entire duration of the follow-up period (median, 285 days; range, 7-455 days; mean, 251 days).

3.5.1 | Short-term outcomes and complications (0-30 days)

Overall, all 8 SUBs were cleared of obstruction with a completely normal SUB irrigation documented after a median of 1.5 tEDTA infusions (range, 1-6; mean, 2.5), documented a median of 10.5 (range, 0.25-14; mean, 8.5) days after starting the first tEDTA infusion.

The schedule of initial irrigations during the first several weeks varied. Three of 8 SUBs received multiple irrigations (range, 2-3) during the first week. All 3 of these SUBs were unobstructed by the end of the week, with a normal SUB irrigation documented after a median of 1 tEDTA infusions (range, 1-2; mean 1.3).

Five of 8 SUBs received only a single therapeutic irrigation on week 1. Of these 5 SUBs, 2 were unobstructed after the initial irrigation, and 3 still were obstructed at the following week reevaluation.

A more frequent infusion protocol was recommended for the 3 persistently obstructed SUBs. One of these 3 SUBs was treated by multiple irrigations in a single week and was unobstructed by 2 irrigations in 3 days. The remaining 2 SUBs were treated by an additional single therapeutic irrigation. These 2 SUBs were found to still be obstructed the following week and the owners opted for multiple irrigations within a single week. These 2 SUBs were finally unobstructed with 4 irrigations in 2 days.

In all cats, after SUB demineralization was achieved, it was recommended to continue the general timeline for further tEDTA infusions as outlined previously, starting with a 1-week reevaluation.

Resolution of renal pelvic dilatation was achieved in the 4 kidneys that initially were obstructed after a median of 2 tEDTA infusions (range, 1-6; mean, 3) over a median of 6 days (range, 2-12; mean, 6.5). Baseline values for renal pelvic width were established individually for each cat based on renal pelvic measurements established 3 months after relief of obstruction.

One cat with bilateral SUBs experienced partial re-obstruction at 19 (right SUB) and 21 days (left SUB) after demineralization with evidence of mild progressive pyelectasia noted on each side during SUB irrigation. This cat was treated using a more frequent tEDTA irrigation schedule for demineralization (3 irrigations per week) compared with its first protocol (2 irrigations per week). During this time, the renal pelvic dilatation resolved, and the SUB could be irrigated normally during the second irrigation performed on the third day. This cat had ionized hypercalcemia at the start of the tEDTA infusions. Additionally, during 1 infusion, 1 device did not passively drain well during tEDTA instillation, causing enlargement of the renal pelvis without appropriate passive decompression. This resulted in cessation of injection after infusing 1.25 mL of tEDTA solution. This event was of no consequence and the renal pelvis passively drained during the next irrigation conducted 5 days later.

One cat was euthanized during hospitalization for cardiovascular disease that was unrelated to SUB mineralization or tEDTA infusion. In this cat, resolution of renal pelvic dilatation and improved renal function were observed compared to the cat's initial presentation.

3.5.2 | Long-term outcomes and complications (>30 days)

Five of 6 cats survived >30 days. The times between irrigations needed to maintain patency of the SUBs were 6 months (1 cat, 2 SUBs), 3 months (2 cats, 2 SUBs), 1 month (1 cat, 1 SUB), and 2 weeks (1 cat, 2 SUBs).

One cat with bilateral SUBs had 2 recurrences of mineralization and re-obstruction on 1 side. The cat's SUB device first re-obstructed 56 days after demineralization and was unobstructed by 2 tEDTA infusions in 1 week. This cat then had a second obstruction 152 days after demineralization that resolved after 5 days of twice daily tEDTA infusions. Patency of the SUBs then could be maintained by biweekly irrigations for 3 months, at which point the client opted for monthly irrigation. After 3 months on the monthly irrigation interval (356 days from initial demineralization), the cat presented on emergency with bilateral ureteral obstructions and an SUB exchange was performed. This cat had a history of idiopathic ionized hypercalcemia before the start of the tEDTA infusions and could not be medically managed because of its demeanor and poor owner compliance. In addition to the 2 ionized hypercalcemic cats that re-obstructed, an additional cat developed intermittent ionized hypercalcemia 1 month after the start of tEDTA infusions but never had any episodes of recurrent mineralization of its SUB.

A second cat (1 SUB) had 1 SUB reobstruction 439 days after demineralization as a consequence of purulent debris accumulation. Urine culture disclosed infection by *Escherichia coli* and *Enterococcus faecalis*. The cat was started on cefpodoxime (7.3 mg/kg PO q24h) along with 2 tEDTA infusions within a week. Because of lack of owner compliance with antibiotic administration, the cat continued to have a chronic UTI and was treated intermittently when symptomatic, without concurrent device obstruction.

Overall, at 3-month follow-up in all cats, the median serum creatinine concentration was 2.4 (range, 2.1-4; mean, 2.7) mg/dL, BUN concentration was 47 (range, 29-60; mean 46) mg/dL, and SDMA concentration was 24.5 (range, 22-26; mean, 26.5) μg/dL. Urine sediment evaluation of 23 urinalyses obtained throughout the protocols indicated evidence of microscopic hematuria in 19 of 23 samples (reference range, <10 RBC/hpf), gross hematuria in 2 of 23 samples, pyuria in 5 of 23 samples (reference range, <10 WBC/hpf), and presence of epithelial cells in 19 samples (19/23).

One cat died 255 days after the start of its infusions unrelated to ureteral obstruction. This cat had diabetes and small cell lymphoma and had stable renal function at the time of death.

4 | DISCUSSION

In our study, infusion of 2% tEDTA solution into the SUB device successfully demineralized and restored patency in all 8 SUBs, after a median of 1.5 infusions (range, 1-6; mean, 2.5) over a median of 10.5 days (range, 0.25-14 days; mean, 8.5 days) with no serious complications observed. Patency of the SUB devices was maintained by varied schedules of tEDTA infusions depending on the cat and client, resulting in 127 tEDTA infusions throughout the duration of the follow-up (median, 285 days; range, 7-455 days; mean, 251.2 days). Although the largest previously published SUB device study noted that 12.7% devices required exchange because of mineralization at a median of 463 days,[1] this rate of device exchange still was lower than that established for recurrence of ureteral obstruction in cats within 1 year after conventional surgical or medical intervention (ie, 40%).[2] Additionally, in the previous study on SUB devices,[1] the use of polyurethane catheters for both the nephrostomy and cystostomy tubes appeared to result in lower mineralization rates (17%) than when the cystostomy catheters were composed of silicone (29%). Although tEDTA infusions into the urinary tract initially were used to prevent chronic infections and promote biofilm breakdown, we unexpectedly noted their ability to resolve occlusions in devices that were not easily irrigated. This observation encouraged further evaluation of this solution for its calcium chelation properties. It is unclear whether the tEDTA was actively dissolving stones completely or decreasing the size of the mineral deposits by chelating calcium, allowing for easier passage within the device or urinary tract.

Original recommendations for postoperative management of the SUB device included a SUB irrigation with sterile saline before discharge from the hospital, followed by routine irrigation at reexaminations at approximately 1 month and every 3 months thereafter.[22,23] Accessing the port of the SUB device serves 4 purposes: (1) to obtain a sterile urine sample without the need for serial cystocentesis on a regular basis (every 3 months), (2) to confirm patency and functionality of the device if necessary, (3) to prevent mineralization of the device by increasing turbulence intermittently during irrigation, and (4) to infuse solutions into the system if and when clinically necessary (eg, tissue plasminogen activator for dissolving blood clots).[1,22] Although the 8 SUBs evaluated in this study are part of a cohort database including 320 SUBs placed at our institution over 10 years, the use of tEDTA only has been implemented for irrigation in the last 30 months and prophylactically

only in the last 24 months. The 8 SUBs described here all were placed a median of 504.5 days before developing occlusion, during a time when prophylactic tEDTA infusions were not part of our standard protocol. Despite the long duration of time these SUBs were implanted, tEDTA was successful in reestablishing patency in all 8 devices.

Of the cats evaluated in our study, only 1 cat was presented with severe acute illness and recurrent ureteral obstruction. This obstruction was immediately relieved by SUB irrigation. Three additional cats (3/8 SUBs) with progressive renal pelvic dilatation identified on ultrasound examination presented during a routine 3-month SUB irrigation without severe acute illness. One of these 3 cats had a history of nonspecific clinical signs (mirtazapine-responsive hyporexia and two episodes of inappropriate urination), but these signs could have been secondary to recent stress associated with the addition of a new family member and not related to the ureteral obstruction. The remaining 4 SUBs that could not be easily irrigated had no evidence of renal pelvic dilatation on the side of the SUB device placement, and it was concluded that either the ureter was patent or only a partial SUB occlusion was present that allowed sufficient urine flow through the device to avoid renal outflow tract obstruction. One cat without renal pelvic dilatation had nonspecific clinical signs (inappropriate urination once every 2 weeks for a month and an episode of inappropriate defecation) that may or may not have been attributable to ureteral obstruction.

We routinely have been irrigating SUB devices using the schedule described here with sterile saline and in the past 10 years have not generally observed relief of obstruction with saline infusion alone. Thus, it is suspected that the chelation properties of tEDTA are responsible for demineralization within the SUB device rather than merely the turbulence of the irrigation protocol. Tetrasodium EDTA has been shown to have increasingly potent chelating effects for heavy metal and mineral cations at increasingly higher pH.[24-26] Addition of sodium ions to a solution containing EDTA salts causes the solubility of the salts and the alkalinity of the solution to increase. Higher alkalinity promotes dissociation of sodium ions from the carboxyl groups in EDTA, driving the formation of tetranegative anions with the ability to chelate heavy metals and minerals such as iron, lead, copper, zinc, cobalt, and calcium.[7-9] The 2% tEDTA solution utilized in our study had a pH of 10.2-10.8, which provided an alkaline environment for increased dissociation of the sodium ions from the tEDTA molecule.[24-26] The subsequent tetranegative anions formed then could complex with calcium to create stable soluble compounds that then were excreted in urine.[7] These chelation mechanisms of EDTA have been shown to break down calcium deposits in vitro and appear to function similarly within the SUB device in vivo.[18,19,21] Because >92% of upper urinary tract stones in cats are composed of calcium oxalate, the chelation of calcium may prove to be particularly useful in cats with upper urinary tract urolithiasis, which has become increasingly prevalent over the past several decades.[1,2,6] Additionally, when we have exchanged SUB devices, analysis of the obstructing material has always identified calcium oxalate (Figure 1).

In our study, the 3 SUBs that received multiple tEDTA irrigations during the initial week all were found to be free of obstruction by the end of the week, with 2 of the 3 becoming patent after a single tEDTA irrigation. In the other 5 SUBs that received only a single irrigation during the initial week, only 2 (2/5) were found to be demineralized on the next reevaluation, whereas 3 (3/5) remained obstructed. Altogether, 50% of the SUBS in our study required only a single tEDTA infusion to achieve demineralization. Of those that remained obstructed, more frequent initial irrigation resulted in more rapid demineralization and fewer subsequent tEDTA infusions. These results suggest that SUBs with mild or partial obstructions can be demineralized with a single tEDTA infusion if client compliance issues or financial concerns exist. However, multiple irrigations during the first week should be recommended for best results with demineralization.

Additional episodes of device re-obstruction and the irrigation interval needed to maintain patency of the device using the 2% tEDTA solution also were evaluated. In the group of cats that survived beyond the short term (5/6 cats), the frequency of tEDTA flushing (T-FloLoc 2% Tetra-EDTA Flush and Lock Solution, Norfolk Vet Products, Skokie, Illinois) required to maintain patency post-obstruction was variable, with frequencies ranging from 1 tEDTA irrigation every 2 weeks to 1 tEDTA irrigation every 6 months. The variability in the irrigation frequency needed to maintain patency could reflect either the individual cat's propensity for stone formation or residual mineralization in the SUB system that could not be removed by the tEDTA irrigation procedure because the time from SUB implantation until implementation of tEDTA irrigation was variable. Cats with more mineral material most likely would require more frequent irrigation because the residual debris could serve as a nidus for more rapid remineralization. In addition, calciuresis was not quantified in each cat, and cats that required more frequent irrigation could have had a higher propensity for urine supersaturation with calcium oxalate.

Of the 2 cats that remineralized their SUBs, 1 had a history of idiopathic ionized hypercalcemia and 1 had intermittent ionized hypercalcemia. The cat with a history of idiopathic ionized hypercalcemia could not be treated medically because of its demeanor, client compliance, and failed dietary intervention. Interestingly, all cats that were not hypercalcemic only had a single mineralization episode. One cat developed hypercalcemia 1 month after starting the tEDTA protocol but did not have any episodes of SUB remineralization. Hypercalcemia has been shown to promote recurrence of calcium oxalate urolithiasis, and in the prior study of 174 SUB devices placed in cats, a statistical association of ionized hypercalcemia and the development of SUB device mineralization was found.[1] In that study, 21% of cats had evidence of ionized hypercalcemia, which was statistically associated with long-term mineralization.[1]

Our study also addresses the safety of the infusion of this formulation of 2% tEDTA. Other studies have found that various other forms of EDTA potentially caused urothelial damage in a variety of animal models.[19,20] In these studies, the urinary tract was intermittently infused with various EDTA formulations for 6 to >20 hours. Chronic chelation of calcium could be toxic to tissues by depleting calcium, and the highly alkaline solution (pH >10) also may cause renal epithelial damage. This is supported by the observation that irrigation

of rabbit bladders using a solution of EDTA saturated with calcium eliminated tissue injury.[19]

In our study, macroscopic hematuria was noted in 2 cats before any tEDTA infusion, which resolved in both cases after irrigation. Renal epithelial cells were noted in 19 of 23 urine samples throughout the study, which may have been a consequence of tissue irritation from the presence or movement of the SUB catheters in the renal pelvis or bladder, or a result of the presence of concurrent nephroureterolithiasis. However, this finding also was present in urine samples obtained before tEDTA infusions, and thus these findings may be unrelated. Additionally, the amount of tEDTA that could be infused in 1 cat was limited by the lack of immediate passive drainage after infusion. This restricted the infusion volume to 1.5 mL instead of 2.0 mL but did not result in any adverse effects for the cat and the problem resolved by the next tEDTA infusion.

Over the course of this study, no increase in serum creatinine or serum SDMA concentration was observed to suggest that infusion of 2% tEDTA had a measurable detrimental effect on renal function. Instead, improvement in median and mean serum creatinine concentrations was observed when comparing initial to 3-month follow-up serum creatinine concentrations (median 2.7 mg/dL initially to 2.4 mg/dL at the 3-month follow-up; mean 3.1 mg/dL initially to 2.7 mg/dL at the 3-month follow-up), and a slight improvement in mean SDMA concentrations (mean 32.7 μg/dL initially to 26.5 μg/dL at the 3-month follow-up; median concentrations were the same between time periods). Additionally, no adverse effects were identified in any cat that had tEDTA infused into its SUB.

The limitations of our study include its retrospective nature, failure to standardize the timing and frequency of each irrigation protocol, and variable duration of time from device placement to first tEDTA irrigation. The frequency and amount of tEDTA infused was established for each cat based on the success of establishing patency, severity of renal pelvic dilatation, severity of azotemia, and client compliance. Additionally, a small number of cats precluded statistical evaluation of the results. Lastly, any cats that presented with severe clinical signs (eg, severe azotemia, severe hydronephrosis, severe hydroureter) with an occluded SUB device were more likely to undergo device exchange than an tEDTA demineralization protocol because of the clinical urgency of the situation and the high morbidity associated with delayed renal decompression.

Overall, infusion of 2% tEDTA solution into the SUB device provided a method for treating the most common complication associated with SUB device implantation (ie, mineralization-associated obstructions). Use of this solution should be considered in SUB device irrigation protocols to help clear mineralized debris and potentially prevent mineralization. Although medical management of calcium oxalate stone recurrence in cats with a SUB device is always recommended, compliance in cats is difficult because concurrent renal disease often precludes the use of stone prevention diets. In addition, the benefits of urinary alkalinization, chelation with potassium citrate, and decreasing calciuresis with hydrochlorothiazide are poorly documented in cats. Thus, prevention of mineralization rather than treatment of mineralization remains the primary goal for managing affected cats, making evaluation of prophylactic use important.

CONFLICT OF INTEREST DECLARATION

Allyson C. Berent and Chick W. Weisse are consultants for Norfolk Vet, which is the company that distributes the SUB device and the TFloLoc 2% tEDTA Solution.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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How to cite this article: Chik C, Berent AC, Weisse CW, Ryder M. Therapeutic use of tetrasodium ethylenediaminetetraacetic acid solution for treatment of subcutaneous ureteral bypass device mineralization in cats. *J Vet Intern Med*. 2019;33:2124–2132. https://doi.org/10.1111/jvim.15582