# Factors associated with positive urine cultures in cats with subcutaneous ureteral bypass (SUB) system implantation.

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**Abstract:**

OBJECTIVES

To report the postoperative incidence of SUB-associated bacteriuria and risk factors in a large population of UK cats, to identify the commonly implicated isolates in these cases and to report associations of positive post-operative urine cultures with device occlusion or need for further surgery.

METHODS

Electronic clinical records were reviewed to identify cats with ureteral obstruction who underwent unilateral or bilateral SUB implantation between September 2011 and September 2019. One hundred and eighteen client-owned cats were included in the study population. Information recorded included signalment, history, surgical and biochemical factors, urinalysis and culture results. Multivariable logistic regression was performed to identify variables associated with a positive post-operative culture.

RESULTS

In total, 8.5% of cats had a positive post-operative culture within one-month post-surgery and 41.2% within one year post-surgery.

Cats with a positive pre-operative culture were significantly more likely to have a positive culture within six months post-operatively (p=0.026 OR 0.245 CI 0.071-0.848). Of the 14 cats with a positive pre-operative culture, six (42.9%) returned a positive culture within one year post-operatively and in four cases (66.7%) the same isolate was identified.

Cats with higher end-anaesthetic rectal temperatures were significantly less likely to return a positive culture within three months (p=0.006 OR 0.398 CI 0.205-0.772) post-surgery. Cats culturing positive for Escherichia coli at any time point (p=0.008 or 4.542 CI 1.485 -13.89) were significantly more likely to have their implant removed or replaced.

CONCLUSIONS AND CLINICAL RELEVANCE

Peri-operative hypothermia and pre-operative positive culture were independent predictors of a post-operative positive culture and this should be taken into consideration when managing these cases. Positive post-operative culture rates were higher than have previously been reported.

**Keywords:** subcutaneous ureteral bypass, SUB, bacteriuria, ureterolithiasis

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## Introduction

Intraluminal ureteral obstruction is an occurrence of increasing incidence in feline medicine; with ureterolithiasis implicated in the majority of cases (1). Ureteral obstruction may also be diagnosed secondary to stricture, stenosis, iatrogenic injury, thrombi and neoplasia (2).

Successful management of ureteral obstruction depends on prompt renal decompression to prevent permanent loss of glomerular filtration capacity (3). Historically where medical treatment failed, nephrectomy was indicated; however in recent years many institutions have adopted ureteral bypass using the SUB system (4) placement as the treatment of choice.

The SUB system consists of two catheters, placed in the renal pelvis and bladder lumen, connected to a shunting port sited in the subcutaneous tissue (4), allowing urine to bypass the affected ureter. SUB placement mortality rates compare favourably to more traditional surgical techniques, with 0% - 13% perioperative mortality reported (5, 6) compared to 18% perioperative mortality for both traditional interventions (1) and ureteral stent placement (6). Intraoperative complications are reported to occur in 7% of cases (5) and perioperative complications necessitating surgical intervention reported in 7% and 9% of cases respectively (5, 6); with device occlusion, device leakage and urethral obstruction most commonly observed.

Bacteriuria following SUB placement is reported in 8-21% of cats (5, 7). Therefore identifying factors predictive of device colonisation and the clinical impact of this may help guide client decision-making.

Risk factors for positive urine cultures in cats with SUB system implantation have previously been described in a small population of 43 cats within an American institution (8), this study population included cats that underwent SUB system or ureteral stent placement. The authors reported that of all variables assessed only use of post-operative antibiosis was associated with likelihood of positive urine culture. Berent et al (2018) reported that both positive pre-operative culture and post-operative use of an indwelling catheter were associated with positive post-operative culture, however other factors were not assessed.

The microbial profile of SUB-system-associated bacteriuria has been reported twice previously (8, 5), both studies from American cat populations. The clinical implications of SUB-associated bacteriuria, in terms of association with device obstruction and requirement for surgical intervention, have not been previously reported.

The objectives of this study were thus threefold. Firstly to report the postoperative incidence of SUB-associated bacteriuria and risk factors in a large population of UK cats; secondly to identify the commonly implicated isolates in these cases; and thirdly to report associations of positive post-operative urine cultures with device occlusion or need for further surgery.

## Materials and methods

Clinical records of all cats with implantation of a SUB system at the Queen Mother Hospital for Small Animal, London between September 2011 and September 2019 were reviewed. Cases were excluded if they had not survived to discharge. Only cases with a minimum of one urine culture performed at least two weeks post-surgery were included. Information recorded included signalment, history, surgical and biochemical factors in addition to urinalysis and culture results. Initial diagnosis of ureteral obstruction was made via abdominal ultrasound performed by board-certified radiologists or residents in training, with pyelography performed to confirm aetiology as required.

Surgery was performed by board-certified surgeons or residents in training, with general anaesthesia supervised by board-certified anaesthetists or residents. A SUB device (Norfolk Vet Products) was implanted as described by the manufacturer (4) under fluoroscopic guidance.

In cats with an active urine sediment, intravenous antibiotic administration was initiated preoperatively; surgery was delayed up to 48 hours during antibiotic treatment if clinical condition allowed. Cats with an active sediment were continued on a therapeutic course of antibiotics for 4-6 weeks post-operatively based upon culture and sensitivity results of urine obtained pre-operatively or from the renal pelvis at surgery.

Cats that survived to discharge were scheduled to revisit the hospital approximately one month post-operatively, at which point a urine sample was collected via aspiration of the subcutaneous port via a sterile technique. Follow-up appointments were then recommended every three months for the first two years and every six months thereafter, when the same technique was performed. From February 2019 standard hospital protocol was revised to include flushing of the systems with 2.5ml of sterile Tetrasodium Ethylenediaminetetraacetic acid (TetraEDTA) per port post sample collection.

Cats with positive urine cultures were generally administered a 3-8 weeks course of appropriate antibiosis based on culture and sensitivity results with culture performed during and at least one week post-treatment. Where empirical antibiosis was required pending culture a 4-6 week course of oral potentiated amoxicillin was prescribed with change of agent as required on return of culture results. Antibiosis was often stopped or not re-prescribed for cats with recurrent or persistent positive urine cultures without lower urinary tract signs

All samples were submitted to the same laboratory. Samples were streaked with an inoculation loop onto MacConkey agar and Columbia agar supplemented with 5% sheep blood. Samples were incubated for up to 24 hours in 5% carbon dioxide at 37 °C.

Bacterial identification was based on Gram-staining, colony type and morphology in addition to routine biochemical testing. Isolate sensitivity was established with the Kirby-Bauer disc diffusion method performed in accordance with Clinical and Laboratory Standards Institute guidelines (9).

Statistical analysis

Descriptive analysis was used for signalment, treatment and sample data. Data were analysed with SPSS version 24 (IBM, Armonk, New York) with significance set at $p<0.05$. Variables were tested for normality using a Shapiro-Wilk test. Normally distributed data is reported as mean, standard deviation, non-Gaussian data is reported as median, range.

A chi-square test was used to compare likelihood of device explantation in bacteriuric cats, between those with clinical signs and those without.

Univariable logistic regression analysis was initially used to assess predictive factors for the following six models; first positive culture results within one (0-30 days), three (0-90 days), six (0-180 days) and 12 (0-365 days) months respectively, for device occlusion at any time point and for device removal at any time-point. Variables for which $p<0.1$ were then further explored using a multivariable analysis, with backward elimination to identify variables for which $p<0.05$.

## Results

One hundred and twenty-four cats had a SUB implanted between the 16$^{th}$ April 2012 and the 6$^{th}$ September 2019, but six cats did not survive to discharge, therefore 118 cats met the inclusion criteria.

Mean age at the time of device placement was 7.17 years (SD: 3.35). Of the 118 cats included in the study, 70 (59.3%) were neutered females, 47 (39.8%) were neutered males and one was an entire male. Breeds representing over 2% of the population are summarised in table 1.

Median body weight at the time of surgery was 4kg (range 2.1-9.7kg), median body condition score was 4/9, (range 1-9).

In 93 cats (78.8%) a SUB system was placed due to ureterolithiasis, four cats (3.4%) presented due to iatrogenic injury (three due to inadvertent ureteral ligation during ovariohysterectomy and one due to stricture formation post ureterotomy), one cat (0.8%) was diagnosed with a ureteral stricture in the absence of ureteroliths or known prior trauma and in 20 cats (16.9%) the underlying pathology was not confirmed.

Forty six (39%) cases had a bilateral system placed and 72 (61%) a unilateral system. Of the unilateral systems 41 (56.9%) were left-sided and 31 (43.1%) right-sided. Median surgical and anaesthesia time were 105 minutes (range 50-275) and 200 minutes (range 125-420) respectively. 64 cats (54.2%) received potentiated amoxicillin peri-operatively, 39 cats (33.1%) received cefuroxime, in 15 cats (12.7%) perioperative antibiotic choice was not recorded.

Cats were hospitalised for a median of 6 days (range 2- 23) post-surgery.

Pre-operative and post-operative (obtained between one and three months post-surgery) clinicopathologic data is summarised in table 2.

One hundred and ten cats had a pre-operative culture performed, of these 14 (12.7%) were positive. Thirteen cultures identified a single isolate and one culture identified two isolates. The most frequent isolates were *E. coli* (42.9%) and *Enterococcus faecalis* (28.6%). Of the 14 cats with positive pre-operative cultures six (42.9%) had a positive post-operative culture, all between day 20 and day 176 post-surgery. Of these six cultures four (66.7%) identified the same isolate both pre and post operatively. Of these four cultures, two isolated *E. coli*, one *E. faecalis* and one *Staphylococcus pseudintermedius.*

At least one month follow-up was available for all 118 cats. Of these, 10 (8.5%) had a first positive post-operative culture within one month post-surgery. The most common organisms isolated were *E. coli* (40%) and *Pseudomonas aeruginosa* (30%). Only one of these 10 cats had had a positive pre-operative urine culture, and the bacteria cultured was different (*E.coli* pre-operatively and *S. pseudintermedius* post-operatively).

A minimum of three months follow-up was available for 112 cats, of these 15 (13.4%) had a first positive culture within three months post-surgery. A minimum of six months follow-up was available for 95 cats, of these 25 (26.3%) had a first positive culture within six months post-surgery. A minimum of one year follow-up was available for 68 cats. Of these 28 (41.2%) had a first positive culture within one year post surgery. Of the first positive cultures returned within the first year post surgery, 23 (82.1%) were single isolates and 5 (17.9%) were mixed cultures of two isolates. The isolates identified in single organism cultures are summarised in Table 3.

Cats with a positive pre-operative culture were significantly more likely to have a positive post-operative culture within six months post-operatively (p=0.026 OR 4.09 CI 1.18-14.18) than those with a negative pre-operative culture in multivariable analyses. This was not statistically significant within one (0.787), three (p=0.935) or 12 (p=0.328) months post-surgery. Of the 14 cats with a positive pre-operative culture six (42.9%) returned a positive culture within one year post-operatively, in four cases (66.7%) the same isolate was identified.

In multivariable analyses cats with higher end-anaesthetic rectal temperatures were significantly less likely to return a positive culture by one month (p=0.010 OR 0.404 CI 0.203-0.803) and three months (p=0.006 OR 0.398 CI 0.205-0.772) post-surgery, but not by six months (p=0.121) or 12 months (p=0.555) post-surgery.

Age, sex, breed, weight, condition score, perioperative antibiotic choice, reason for device placement, outdoor access, pre-operative urea, creatinine, urine pH and specific gravity, length of hospitalisation, anaesthetic and surgery were not significantly correlated with likelihood of returning a positive culture at any time-point when investigated with univariable analysis (all $p>0.1$) and were not included in the multivariable model.

Use of TetraEDTA as part of a maintenance protocol from one-month post-surgery was not significantly correlated with likelihood of returning a positive culture within three months post-operatively and was not included in this multivariable model.

Site of implant and sex were included in the multivariable regression analysis but were not statistically associated with likelihood of returning a positive culture at any time-point ($p>0.05$).

Of the 28 cats returning positive urine cultures within 12 months post-surgery, 10 (35.7%) were asymptomatic with no noted device complications, two (7.1%) were asymptomatic with device obstruction diagnosed on imaging, 11 (39.3%) had lower urinary tract signs and/or secondary pyelonephritis and five (17.9%) had transient lower urinary tract signs, which were at times absent in the presence of bacteriuria.

11 cats with a positive culture had their implants removed or replaced, of these seven (63.6%) had either transient or perpetual clinical signs and four (36.4%) were asymptomatic. 17 cats with a positive culture did not have their devices removed, of these nine (52.9%) had transient or perpetual clinical signs and eight (47.1%) were

asymptomatic. There was no significant association between presence of clinical signs and likelihood of device removal in cats with bacteriuria (p=0.539).

In total 26 devices became obstructed over the period studied in 22 cats (18.6%): 18 (15.3%) due to device mineralisation, seven (5.9%) due to a catheter kink, and one (0.8%) due to a blood clot. Of the 18 devices (17 cats) with mineralised obstructions nine were revised or replaced, three cats were euthanased and five declined surgical intervention due to minimal or absent clinical signs.

Nineteen (16.1%) of the devices were removed or replaced, nine (47.4%) due to device obstruction, 10 (52.6%) due to persistent infection that could not be eliminated with antibiosis and one (5.3%) due to a combination of infection and obstruction.

Cats culturing positive for *E.coli* at any time point (p=0.008 OR 4.542 CI 1.485 -13.89) were significantly more likely to have their implant removed or replaced when investigated with multivariable analysis. This was not significant for cats culturing positive for *P. aeruginosa* (p=0.09) or *E. faecalis* (p=0.059) when investigated with multivariable analysis, or cats with positive cultures pre-operatively or within any time point post-operatively when investigated with univariable analysis (p>0.1).

Cats with a positive urine culture pre-operatively or within any time-point post-operatively were not significantly more likely to develop a device occlusion than cats without a positive culture at any time-point when investigated with univariable analysis ($p<0.1$). However cats with *P. aeruginosa* cultured at any time-point post-operatively were significantly more likely to develop an implant obstruction ($p=0.033$ OR 5.0 CI 1.138-21.98), this was not significant for *E.coli* ($p=0.583$) or *E. faecalis* ($p=0.532$) positive cultures when investigated with multivariable analysis.

## Discussion

This study presents the results from a large number of urine cultures collected from cats with SUB systems placed in a UK referral centre over an eight year period. Positive cultures were obtained from 41.2% of the cats at some time point within twelve-months post-operatively, with 8.5% returning a positive culture within one-month post-operatively.

A previous paper by Kopecny et al (2019) reported 25% of cats returned a positive post-operative urine culture, however it is difficult to compare these results with those reported here as the population studied included cats with ureteral stent placement, the time points assessed were different and only six of 48 samples were collected via sterile subcutaneous port aspiration. It is also interesting to note that this paper reported only 2.1% of cats returned a positive pre-operative culture compared to 12.7% of the cases reviewed here, 0% of the cases reported by Wolff et al (2016) and 25% of the cases reported by Berent et al (2018). The latter papers reported a post-operative positive culture rate of 21% within ten days post operatively (7) and 24% at any time point (5), however again direct comparison is challenging due to the differences in data handling and proportion of cases lost to follow-up. Discrepancies may also reflect difference in sampling methods or previous management of the cats presented for surgery.

The most commonly cultured isolate in this study, both pre-operatively and at any time point post-surgery, was *E.coli.* Berent et al (2018) also reported *E.coli* as the predominant isolate cultured from pre-operative urine collection, however, in both that paper and Kopecny et al (2019) *E. faecalis* was reported as the most common isolate cultured from post-operative samples. *E.coli* and *E. faecalis* are both commensals of the feline gastrointestinal tract (10) and thus the most likely mechanism of urinary tract infection is ascending colonisation by pre-existing enteric microflora. In this study, *P. aeruginosa* was the second most commonly cultured organism at one month and joint second most commonly cultured organism (in addition to *E. faecalis*) at 12-months post-surgery. *P. aeruginosa* is a ubiquitous environmental organism, commonly implicated in opportunistic nosocomial infections

(11), in this study culturing *P. aeruginosa* at any time point was significantly associated with risk of device obstruction, although not significantly associated with device removal. This discrepancy is likely due to clients declining removal due to financial constraints, or because the native ureter(s) had regained patency and the infection was subclinical or resulting in only mild clinical signs.

The only factors identified as predictive of post-operative positive culture were positive pre-operative culture and lower end-anaesthetic rectal temperature. In this cohort four of the 14 cats with a positive pre-surgical urine culture cultured positive for the same isolate within 176 days post-surgery. Berent et al (2018) also demonstrated that pre-operative bacteriuria was significantly associated with post-operative bacteriuria, however in this study it is not clear what proportion of cats returned the same isolate at both cultures. Perioperative hypothermia has not previously been investigated as a risk factor for post-operative implant infection, Beal et al (2000) assessed the effect of hypothermia on surgical site infection rates in dogs and cats, and found no significant relationship, however this paper reported incision infections, rather than implant associated infections.

In human patients perioperative hypothermia has been shown to be associated with surgical wound infections. It is thought that this occurs due to induction of peripheral vasoconstriction leading to reduced tissue oxygenation and subsequent impaired chemotaxis, phagocytosis, and antibody production (13). In one study of human patients undergoing colorectal surgery, core temperature at end of surgery was highly correlated with wound infection up to two weeks post-surgery, with 19% incidence in the hypothermic group compared to 6% in the normothermic group (14). In our study hypothermia was associated with increased risk of bacteriuria up to three months post-surgery, it is possible that later positive cultures represent initial false negative cultures or subclinical cases who missed the one month recheck.

In this study *E.coli* was associated with need for device removal/replacement. This finding highlights the clinical significance of bacterial colonisation in these cases. In the cases reviewed here the most common reason for implant removal/replacement was bacterial infection. This is in contrast to previous work which reported mineralisation to be the most frequent reason for device exchange, causing occlusion in 24.2% of devices (5). In our study population occlusion due to device mineralisation occurred in only 15.3% of cases and led to device removal or replacement in only 8.5% of cats. The discrepancy in these figures may be attributable to multiple factors, such as differences in diet and water mineralisation levels.

In this population clinical signs were seen in 57.2% of cats with positive urine cultures, but only 39.3% of cats showed persistent lower urinary tract signs or pyelonephritis, suggesting that many cats with positive urine cultures after device placement are not clinically affected, i.e. have subclinical bacteriuria. This reflects previous work by Berent et al (2018) (5) in which only 62.5% of persistently affected cats had clinical signs suggestive of a urinary tract infection. The optimal way to manage cats with SUB implants and positive urine cultures without lower urinary tract signs remains a topic of debate. In this study the presence of any lower urinary tract signs was not associated with an increased likelihood of device removal, but for some of these cats the clinical signs were only transient and overall case numbers for cats with positive urine cultures were small. Further work to investigate the optimal management strategies for cats with SUB implants and positive urine cultures, both symptomatic and subclinical, are warranted.

Our post-operative maintenance protocol was changed in February 2019 to include instillation of TetraEDTA into the devices following sample collection. In this population there was no significant difference in likelihood of returning a positive culture at three months post-operatively for cats receiving routine TetraEDTA flushing compared to those which did not. Correlation with positive culture at later time-points post-surgery could not be investigated in this population as timing of data collection meant follow-up length was limited in cats receiving the updated protocol; however, this is an area which warrants further investigation.

The main limitations of this study are attributable to its retrospective design, with available follow-up and pre-operative details variable. Although revisits were advised at standardised intervals many patients did not revisit when advised. Additionally cultures reported here may represent either clinical urinary tract infections or subclinical bacteriuria. Although an attempt has been made to retrospectively classify the cats as asymptomatic or otherwise, this distinction was made by reviewing historical data which may not have been complete. Equally categories were not always clearly defined, e.g. some cases showed transient clinical signs which waxed and waned independent of treatment whereas others had persistent signs.

In conclusion post-operative bacteriuria occurred at least once within 12 months post-operatively in 41.2% of cats and was a risk factor for device removal/replacement. Both peri-operative hypothermia and post-operative positive culture were predictive of post-operative positive culture and this should be taken into consideration when managing these cases.

Statements

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This work involved the use of non-experimental animals only (including owned or unowned animals and data from prospective or retrospective studies). Established internationally recognised high standards ('best practice') of individual veterinary clinical patient care were followed. Ethical approval was granted by the RVC ethical approval board, submission reference SR2017-1364

Informed consent (either verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (either experimental or non-experimental animals) for the procedure(s) undertaken

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