1 2 3	A CLOSER LOOK AT THE HEALTH OF CATS SHOWING URINARY HOUSE SOILING (PERIURIA): A CASE-CONTROL STUDY
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Abstract

47	Objective: Perform a case-control medical evaluation of cats from multi-cat households presenting with
48	inappropriate latrining and spraying behavior.
49	Methods: Owners of 18 spraying and 23 latrining cats with normal control subjects available from the
50	same households were recruited for a case-control study. Otherwise overtly healthy dyads were brought
51	together to the veterinary hospital of the University of São Paulo, for a medical work-up (i.e. physical
52	examination, complete blood count, biochemical profile, urinalysis and urine culture, abdominal
53	ultrasound of the urinary system and in females, where possible, cystoscopy).
54	Results: Medical problems were identified with similar frequency in the "sprayers" (38.9%) "latriners"
55	(39.1%) and controls of the <i>latrining</i> group (26.1%) but not the spraying group (5.5%). The difference
56	between cases and controls from spraying households was significant. Common potential health related
57	changes include renal insufficiency, cystitis, bladder lithiasis. Renal calculi, higher creatinine levels
58	(within normal reference range) and "glomerulations" (detected during cystoscopy) were also found in
59	the remaining "sprayers" and "latriners" who were considered healthy. Post-cystoscopy a new form of
60	periuria occurred in two cats (one "sprayer" and one "latriner").
61	Conclusions and Relevance: These results indicate that spraying or latrining behaviour in the home, as
62	well as living with a cat who is not using the litter box as a latrine, are all associated with a higher level
63	of urinary tract abnormalities, but not living with a cat who is spraying. The findings also suggest that
64	both forms of periuria might be associated with interstitial cystitis. We therefore conclude that all cats
65	with periuria need to be carefully evaluated medically and that treatment of latrine related problems
66	should consider all cats in the house, whereas spraying may be more focused on the individual
67	displaying the problem.
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Key-words: marking, spraying, toileting, latrining, disease, feline, cystoscopy

1. INTRODUCTION

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In the clinical context, *spraying* for marking purposes by domestic cats has long been distinguished from inappropriate urinary latrine related behavior (*latrining*) (1,2,3,4,5,6,7,8). *Spraying* commonly involves urine deposited on vertical surfaces (or on significant horizontal spots) with the cat typically in a standing posture (2,4,5). "Sprayer" cats generally keep use of the appropriate latrine for both urination and defecation (2,4,5). By contrast, inappropriate *latrining* is mostly characterized by large amounts of urine, usually on horizontal surfaces with the cat in a squatting posture (2,4,5). "Latriner" cats may give up using the latrine and so both urine and faeces may be found in inappropriate locations (2,4,5).

Successful management of either condition depends on the identification of medical factors which might be contributing to the problem (1,2,3,4,5,6,7,8). The evidence for the significance of medical problems in these cases is inconsistent (9, 10), and largely based on simple case reports and comparisons, with inadequate controls for things like differences in management that might exist (11). Nonetheless, the overall recommendation of adequate medical screening in order to eliminate potential medical factors contributing to the problem, remains sound advice (1,2,3,4,5,6,7,8). Some suggest that the urination behaviour of cats with a urinary problem does not resemble urine marking, and urinalysis does not provide relevant diagnostic information, at least in cases of urine spraying (12), but urinalysis may be of value in cases of latrine related problems (12). It is also worth noting that in many cases of periuria (problematic deposition of urine in the home regardless of cause), the medical assessment is often quite superficial, frequently based on only a brief physical exam and possibly urinalysis (12). A more complete evaluation of the urinary system (e.g. via ultrasound or cystoscopy) may reveal further abnormalities (13). Indeed, the frequency and extent to which medical evaluations are made in these cases is not known. Thus it is not possible to say with any confidence, what problems are present in these cases or what their relevance might be. Current practice focuses on the behavioural history, with the precise role of urinary system abnormalities evaluated to a variable extent for their relevance on a case by case basis.

Veterinary behavioural guidelines not only propose diagnostic procedures but also treatment protocols, for both inappropriate *latrining* behaviour and *spraying*. Although these are generally clear and reasonably easy to apply, complete eradication of the problem using only management and environmental change is often unsuccessful (14). There is clearly a proportion of refractory cases in

which typical management regimes do not work. This may include those with untreated medical complications, and so it is important to improve our understanding of the potential relationship between and role of urinary tract abnormalities in these cases.

Therefore this study aimed to address some of the shortcomings identified in previous reports of the association between urinary tract disease and periuria by performing an in-depth medical evaluation of a series of cats from multi-cat households presenting with inappropriate *latrining* and *spraying* behaviour alongside control subjects drawn from the same household in order to control for management confounds between subjects (15).

2. MATERIAL AND METHODS

2.1. Recruitment and Selection

Publicity aimed at selecting house soiling cats and matched controls (without periuria) from the same multi-cat households (n=3-9 cats per house) was promoted in several ways: via a poster at the veterinary college at the University of São Paulo (FMVZ/USP) and several veterinary clinics in Sao Paulo and neighboring cities, emails to a list of students of the veterinary college, postings on cat breeder websites and Internet communities related to pet cats.

Cats reported by their owners to manifest periuria were classified into *spraying* or *latrining* groups (together with their respective controls without periuria) on the basis of a careful behaviour analysis made by a veterinary behaviourist considering cat posture and behaviour repertoire when depositing urine outside the litterbox, location, target and amount of urine deposited outside the litterbox, litterbox use, etc. Households where different cats exhibited urine *spraying* and *latrine related behaviour* in the home were not eligible for inclusion. This means that in selected *spraying* households there was no *latrining* behaviour in the home by any of the cats; similarly, in the selected *latrining* households a *spraying* problem was absent.

Problem behavior (i.e. spraying or latrining) had been manifested by participant cats from months to years with unsuccessful treatment attempts made by most of the owners previously to the current study. During the study, with the exception of the cases further described in the paper, cats did not receive any treatment for their problem behaviour.

134 2.1.1 Spraying Group

Twenty-one urine *spraying* "case-control" dyads were initially recruited, but in the case of three dyads examinations could not be concluded for various reasons (e.g. cat became sick) and therefore they were excluded from further involvement in the research. The remaining 18 "case-control" dyads were then subjected to medical examinations involving a complete blood count, biochemical profile, urine exam and urine culture and ultrasonic evaluation of the urinary system at the university veterinary hospital (HOVET-USP).

Among the 18 "case" cats, there were 3 females and 15 males; 17 mixed-breeds and one Persian, with average age 6.27 years (SD=2.44). "Control" cats were 6 females and 12 males; 17 mixed-breeds and one Siamese, with average age 6.43 years old (SD=4.48). On average, there were 6.09 cats per household (range: 3-8 cats). Four of the 18 "case-control" dyads came from two households; there were therefore 16 different households in this Group. *Spraying* households were all houses (as opposed to flats) and half of them offered free outside access to the cats.

2.1.2 Latrining Group

Twenty-nine inappropriate *latrining* "case-control" dyads were initially recruited but for six dyads the examinations could not be concluded (e.g. owner did not fast in the cat or did not prevent the litterbox use and so cat did not have sufficient urine for the exams). The remaining 23 "case-control" dyads were then submitted to similar clinical examinations at the university veterinary hospital (HOVET-USP).

Of the selected 23 "case-control" dyads, 18 "case" cats were females and 5 males; 13 mixed-breeds, 4 Persians, 4 Maine Coons and 2 Ragdolls. Their average age was 4.46 years (SD=2.19). Among the "control" cats, there were 13 females and 10 males; 16 of mixed-breed, 4 Maine Coons and 3 Persian. Their average age was 5.21 years old (SD=3.35). Households in this group had on average 4.6 cats (range: 3-8 cats). Four of the 23 "case-control" dyads came from two households, and so there were 21 different households in the group. Toileting households were evenly split between houses and flats and none of the toileting households offered free outside access to the cats.

2.2. Medical Exams

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2.3. Cystoscopy

the dyad from further analysis.

Second visits to the veterinary hospital were planned for cystoscopies of suitable female cats, subject to owner informed consent, including explanation of the need for a general anaesthetic. Cystoscopies were carried out on selected female "case" cats only (i.e. those exhibiting periuria without medical abnormality of concern in the preliminary exams). This cystoscopy allowed us to investigate abnormalities that may have passed unnoticed in the previous exams (e.g. interstitial cystitis) (13).

All procedures involved in the medical examination were conducted on both "case" and "control"

cats from the household on the same morning, with cats having fasted for between 8 and 12 hours. The

collected materials were processed according to standards and techniques established by the Laboratory

of Clinical Pathology (HOVET-USP). Ultrasounds were performed in the same room, by a specialist in

veterinary ultrasonography; a second veterinary feline specialist carried out all other clinical

In the 2 hours immediately preceding the exams, owners were instructed to encourage water intake,

and to prevent the use of the litterbox in an attempt to promote bladder filling, necessary for the

collection of urine, which was done by cystocentesis guided by ultrasound. Blood samples had to be

sufficient for at least a complete blood count and biochemistry profile, otherwise the dyad was

Any abnormality of the lower urinary tract (e.g. bladder urolithiasis, cystitis) or alterations

indicative of either systemic disease or organ dysfunction was considered a medical abnormality; the

dyad did not then progress further in order to avoid undue stress, following the establishment of a

medical problem of concern. However, alterations of the upper urinary tract which, did not appear to

interfere with functioning of the urinary system (e.g. renal urolithiasis accompanied by normal

urinalysis and renal profile) although considered potentially problematic, did not result in exclusion of

Out of the 23 potential "case-control" dyads reaching this stage, 12 (2 from the Spraying Group and 10 from the Latrining Group 2) included female "case" cats, suitable for cystoscopic examination and 8 owners elected for cystoscopy.

Cystoscopies were performed by the same specialist as the clinical exams following fasting for at least 8 hours (maximum of twelve hours) and withdrawal of water 2 hours before the exam. Cats were pretreated with acepromazine and meperidine (0.05mg/kg and 4mg/kg, respectively, IM). Anesthesia was then induced with propofol (5-6 mg/kg, IV) and maintained with isoflurane diluted in 100% oxygen at concentrations necessary to maintain the third level of the third stage of Guedel's classification of depth of anesthesia (16). In the case of three females which appeared to be aggressive, ketamine (2 mg/kg IV) was added to the premedication, which allowed us to safely handle them whilst promoting induction with propofol. In the last four procedures, in order to achieve a better penetration of the endoscope via a deeper urethral relaxation, butorphanol (0.4 mg/kg IV) was added to the protocol.

2.4. Statistical Analysis

A Shapiro-Wilks normality test was first performed for each of the medical variables in both groups ("cases" and "controls" were first tested separately). In the event of a normal distribution for both "cases" and "controls", Student paired t-tests were used for pairwise comparisons, with Wilcoxon signed-rank tests used in the case of non-normally distributed data.

The prevalence of medical alterations in "case" versus "control" cats in both *spraying* and inappropriate *latrining* dyads was compared by either Fisher exact test or Pearson Chi² test. Similarly, comparisons of case subjects between groups were also assessed using Pearson Chi² test. Statistical analysis was performed using SAS software (9.2 version) with a probability level of 0.05 used to assess significance.

3. RESULTS

3.1. Spraying dyads

Medical exams revealed that out of 18 apparent healthy cats exhibiting urine *spraying*, 7 (38.9%) demonstrated medical alterations; but this was found in only one control cat (5.5%). Significantly more "case" than "control" cats (Fisher exact test, p=0.041) therefore had at least one of the following medical conditions: renal insufficiency (2), idiopathic cystitis (2), diabetes insipidus (1), diabetes mellitus (1), ectopic testes (1). The only control cat with a medical alteration presented with bladder lithiasis.

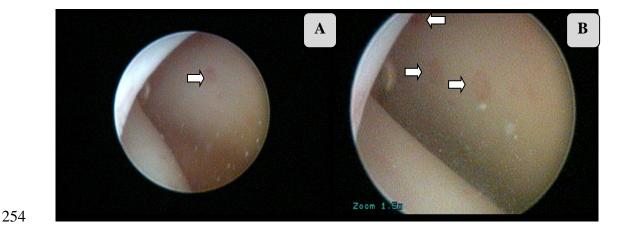
The remaining 11 dyads were considered clinically healthy on the basis of the initial health screen, although some medical complications which did not obviously impair either urinary or other system functioning were identified. In 4 "case" and 1 "control" cat, renal lithiasis was identified (these measured about 0.3 cm and in all cases were located in the renal pelvis); a renal cyst was found in a fifth "case" cat. One "case "and one "control" showed renal diverticulum calcification. This meant that 12 out of the initial 18 recruited "sprayers" (i.e. 66.7%) and 3 out of 18 (i.e. 16.7%) controls had identifiable deviations from a perfect state of the urinary tract. One of the remaining "case" cats had glycosuria, but blood levels of glucose as well as frutosamine were within normal reference range. Leucocytes count was high (i.e. 19,900 cells/mm³) and further urinalysis did not reveal glycosuria suggesting the condition was not due to diabetes mellitus.

Blood leucocyte counts of "cases" and "controls" (n=11) did not differ significantly (median +/- IQR: "case" cats = 13,700 +/- 3,800 cells/mm³, controls = 10,700 +/- 13,200 cells/mm³; p = 0.6377). However, serum creatinine levels were significantly higher for *sprayers* in comparison with their "controls" (mean+/-SD: "case" cats = 1.53+/- 0.31mg/dL controls = 1.19+/-0.23mg/dL p=0.005). With regard to blood urea, the difference between "cases" and "controls" approached significance (mean+/-SD: "case" cats = 62.68+/-6.13mg/dL controls = 56.35+/-6.41mg/dL p=0.0597).

Cystoscopy performed in one of the two *spraying* female cats revealed several scattered submucosal petechiae ("glomerulations") (Figure 1), oedema and mild bladder haemorrhage, indicative of interstitial cystitis.

<u>Follow-up:</u> over the days following cystoscopy, the cat with petechiae showed hematuria, polakiuria and apparently painful urination. A latrine related problem arose with the cat depositing urine containing blood in the bathroom sink (such a behaviour had never been observed before). This lasted a couple of weeks and the owner felt that the problem had been exacerbated by the cystoscopic examination. The cat was successfully treated with amitriptyline (1mg/kg, BID) from the first day after cystoscopy for 60 days; the cat returned to using the litterbox for latrine related urination with the owner reporting only rare occasions of urine *spraying*. Such improvement was sustained for at least 6 months when the last contact with the owner occurred.

Figure 1. Cystoscopic examination of a female "sprayer" cat. White arrows indicate petechiae (A – normal size; B – 1.5X zoom).



3.2. Latrining dyads

Medical exams revealed that out of 23 apparently healthy cats exhibiting inappropriate *latrine* behaviour, 9 (39.1%) demonstrated an overt medical concern; this was found in 6 control cats (26.1%). The difference was not significant between "case" and "control" cats (Pearson Chi² test, p=0.365). Medical problems found among cases were: renal insufficiency (3), leucocytosis (2), leucocytosis plus bladder plug (1), bladder lithiasis (1), bladder plug (1), hepatic disease (1). "Control" cats had leukaemia (1), bladder diverticulum (1), renal insufficiency (1), bladder lithiasis (1), abdominal liquid (1), hepatic disease plus urinary infection (1).

Of the 12 remaining dyads considered healthy on the basis of the initial health screen, there were a range of other conditions identified which were not considered to obviously impair either urinary or other organic system functioning. Four "case" and 4 "control" cats had one of the following alterations in the ultra-sound image of their kidneys: diverticulum calcification, heterogenous texture, decrease cortico-medullary definition, retraction and/or thinning of cortical area leading to loss of kidney definition. This meant that in total 13 out of the initial 23 recruited "latriners" (56.5%) had abnormalities and 10 out of 23 controls (43.5%).

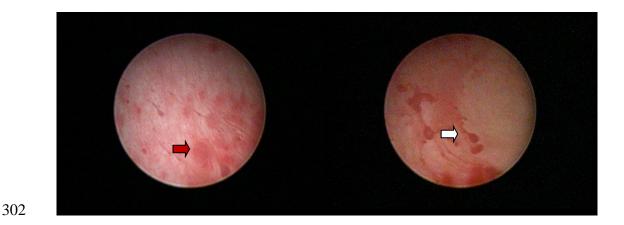
One "control" cat had glycosuria, but blood levels of glucose and frutosamine were within normal reference ranges and leucocytes count was high (i.e. 30,100 cells/mm³). Later further urinalysis did not reveal glycosuria suggesting that the cat did not have diabetes mellitus.

Blood leucocyte counts for "cases" and "controls" (n=12) did not significantly differ (mean+/-SD: "case" cats = 10,641.67+/-2,191.91 cells/mm³, controls = 13,308.33 +/- 7,206.87 cells/mm³; p = 0.229). Serum creatinine as well as urea levels were also not significantly different when "latriners" were compared with their controls (mean+/-SD, creatinine: "case" cats = 1.38+/-0.15mg/dL, controls = 1.40+/-0.26mg/dL p=0.848; urea: "case" cats = 60.28+/-15.58mg/dL controls = 60.13+/-12.66mg/dL p=0.968).

Cystoscopy was attempted on 6 of the 10 potentially qualifying female cats, but complete bladder visualization was possible in only 3 of them; in the other 3 cats, urethra passage was very difficult and given the risk of injury, the procedure was abandoned. The bladder was healthy in 2 cats, but in the third there were submucosal petechiae ("glomerulations"), ulcerations and haemorrhage (Figure 2) indicative of interstitial cystitis.

<u>Follow-up:</u> on the days following cystoscopy the cat diagnosed with interstitial cystitis showed hematuria, polakiuria and painful urination (including high pitch vocalization before entering the litter box). Urine *spraying*, which had never been observed in this cat before as well as a digging behaviour at the front door of the house (followed by urination just there) arose during this time. This cat was treated with amitriptyline (1mg/kg, BID) from the first day after cystoscopy and for 90 days. Within a couple of weeks, the cat returned to its previous pattern of eliminating large amounts of urine on horizontal surfaces in the home without signs of pain. The owner reported, however, a decrease in frequency of inappropriate urination. The problem was still present after 6 months despite inclusion of behaviour therapy to augment treatment.

Figure 2. Cystoscopic examination of a female "latriner" cat. Red arrow indicates petechiae and ulceration; white arrow indicates haemorrhage.



3.3. Comparison between "Sprayers" and "Latriners"

Medical conditions were detected with similar frequency in both apparently healthy "sprayers" and "latriners" (Pearson Chi 2 test, p= 0.639).

4. DISCUSSION

Medical conditions were common in both overtly healthy "sprayers" and "latriners", thus, despite recommendations to focus on ruling out medical problems in cases of inappropriate *latrining* only (12), our findings from the case-control study emphasize that a medical work-up should be undertaken in any case of periuria as previously suggested (10). This finding is supported by two cases who went on to develop periuria one in the form of spraying the other in the form of latrining, following cystoscopy. The prevalence of medical conditions among our selected sprayers is more in agreement with the findings of Frank et al (10), Barcelos et al (11) and Tynes et al (12) than the report of Landsberg and Wilson (17). The differences could be due to which medical conditions are considered as possibly interfering with the act of urine expulsion. In the study reported here, any alteration of the upper urinary system potentially compromising urinary function, any abnormality of the lower urinary tract or altered functioning of the organism in general that was considered as possibly linked to periuria led to a medical concern for the cat; by contrast, other studies have only considered lower urinary tract disorders or the result of a single urinalysis as exclusionary criteria (12,17). In the case of "latriners", the percentage of cats presenting a medical condition (i.e. 32.1%) is consistent with previous research which has indicated a similar lifetime prevalence of urinary tract disease (9,11,18).

Physical alterations in periuric cats are typically described in relation to *lower* urinary tract disorders or other conditions known to be painful (4,5,8,9,12, 18), but alterations in the *upper* urinary

tract were seen in both "sprayers" and "latriners" subject to more intense medical evaluation. The significance of this remains unclear. Investigations on the link between renal alterations as early renal disease and different types of urinary act, particularly when urinary function does not seem to be diminished are lacking. Likewise, the potential for renal formations (e.g. calculi within the kidney) to cause pain and as a consequence change urination behaviour has been completely overlooked in the scientific literature. Thus, if such conditions act either as causes or contributors to inappropriate urination (particularly in the *spraying* cases) and have not been detected due to medical exams being focused on the lower urinary tract, this might explain, at least in part, the refractoriness of some cases: since part of the problem has not been recognised and managed. Since the veterinary goal is to provide complete care for the feline patient with a urinary behaviour problem (4,5,8), a detailed medical examination including imaging evaluation of the upper urinary tract should be encouraged, especially in refractory cases. Therapeutic intervention for some conditions (e.g. evidence of CKD-stage 1, renal calculi, renal cyst) may not involve much more than monitoring the condition, since the significance of these features to wider kidney disease progression is still unclear (19); a relapse in periuria correlated with medical progression, or an improvement in association with medical treatment, may help to establish a link between these conditions, and help to explain why a refractory case has not achieved success despite the appropriate behaviour management.

In *spraying* households medical conditions were more common in "sprayers" than in "controls" whereas in *latrining* households "latriners" and "controls" were equally affected by medical problems. A 21.4% prevalence of medical problems among "control" cats in the *latrining* group was unexpected; a previous report of 100 apparently clinically healthy cats has indicated that only 6% had medical problems (e.g. hyperthyroidism, urinary infection)*. The current report is the first time medical problems have been identified with such high frequency in cats sharing the same environment as those with a latrine problem. Nonetheless, the relatively high prevalence of abnormalities in control cats from households with a latrine cat, is similar to the general prevalence reported by Tynes et al. (12) and lifetime owner-reported history prevalence or urinary disease reported recently by Barcelos et al. (11). One possible explanation for such a result lies in environmental physical and/or social characteristics (or even ownership style) which may predispose all household cats to diseases in *latrining* households. For example, Barcelos et al. (11) recently reported that cats with a latrine problem were less likely to be

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¹*Garcia JL, Bruyette DS. American College of Veterinary Internal Medicine Forum poster session. 1998.

described as having a heavy dependence on their owner compared to either spraying cats or non-periuric controls.

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Spraying households had a higher average number of resident cats than latrining houses. Although this had not reached significance we can hypothesized that cats from spraying houses were more likely to be involved in conflict behaviours and therefore more prone to manifest spraying but not necessarily to develop more diseases. It should also be noted that cats in *latrining* houses did not have outside access whereas half of spraying households offered free outside access to the cats, and this has been identified as a risk factor for the condition (11). We hypothesise that a lack of access to diverse external latrines might reduce urinary frequency and thus encourage overdistension of the bladder, predisposing subjects to cystitis. Depending upon combinations of external factors (e.g. decrease in water availability, provision of a low quality diet) and individual predispositions, medical problems interfering with the urinary system may also arise, potentially leading to periuria in some subjects. In other cases, non-urinary illness may develop and likely result in other medical signs which may not be perceived by the owner of multiple-cats, at least in its early stages. Thus, we suggest that there may be several ways in which the care needed for optimal bladder health may not be provided by the owners of participant cats in the *latrining* group. Whether this is a problem of the households in this study only, or if it represents a wider characteristic in cases of latrining cats remains to be explored, although the recent results of Barcelos et al. (11) suggest it may be a much wider problem. In the interests of caution to safeguard cat health and welfare, we therefore suggest clinicians make a broader enquiry into the overall environmental management and general feline urinary health care of households affected by a latrining problem. This should emphasise the importance of multiple litter tray sites in all homes, with indoor only cats (regardless of the number of cats in the household), but perhaps for a slightly different reason than is commonly described in behaviour texts (1,2,4,5,6,8); i.e. to maintain bladder health rather than meet the desire of cats not to share a latrine with others. Although issues such as unacceptable cleanliness of the litterbox, inappropriate distribution of the litterboxes etc may play a role (1,2,4,5,6,8), it is worth noting that litter box features were not a risk factor in the recent study of Barcelos et al. (11), although lack of access to outdoor latrines was. Perhaps too much emphasis has been put on hygiene and odour related issues, when it may be more appropriate to focus on choice and opportunity for cats.

Cystoscopy provides an accurate way to diagnose cystitis and its use in this study reflects the value of a more multimodal veterinary medical approach to behaviour cases (20,21,22,23,24,25). However, as professionals it is important for veterinarians to offer expert advice which balances the risks with the benefits of any proposed procedure. We do not recommend cystoscopy for all female cases of inappropriate urination. There are risks from anaesthesia, possible complications (including those illustrated here) and cost factors to consider, alongside a recognition that full inspection of the bladder is not possible in all cases (25). It should also be recognised as a highly specialised procedure (26,27). However we do suggest that cystoscopy may be valuable in refractory, atypical and more obscure cases. Before cystoscopy, owners must be made aware of the procedure itself as well as the risk of temporary worsening of the problem or a new form of periuria, as appeared to occur in two cases in this study.

5. CONCLUSIONS

In conclusion, our findings emphasise the importance of considering not just bladder health but general urinary tract functioning in all cats with periuria. For those showing a latrine problem in the home, we suggest that attention needs to be paid to the provision of sufficient latrine opportunities as a first line of enquiry. Further work is required to establish the nature of the causal link between urinary tract problems and periuria, and this will likely be accelerated by greater co-operation between internal medicine and behavioural specialists.

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 $CONFLICT\ OF\ INTEREST\ -\ Authors\ declare\ no\ potential\ conflicts\ of\ interest\ with\ respect\ to\ the\ research,\ authorship,\ and/or\ publication\ of\ this\ article.$

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