

# *Corynebacterium urealyticum* urinary tract infection in dogs and cats: 7 cases (1996–2003)

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**Objective**—To identify clinical features of *Corynebacterium urealyticum* urinary tract infection in dogs and cats and antimicrobial susceptibility patterns of *C urealyticum* isolates.

**Design**—Retrospective study.

**Animals**—5 dogs and 2 cats.

**Procedure**—Medical records of dogs and cats for which *C urealyticum* was isolated from urine samples were reviewed. Isolates from clinical cases, along with previously lyophilized untyped isolates of *Corynebacterium* spp collected between 1977 and 1995, were examined and, if subtyped as *C urealyticum*, tested for antimicrobial susceptibility.

**Results**—Signalment of infected animals was variable. Prior micturition disorders were common, and all animals had signs of lower urinary tract disease at the time *C urealyticum* infection was diagnosed. Median urine pH was 8.0; WBCs and bacteria were variably seen in urine sediment. In vitro antimicrobial susceptibility testing of 14 *C urealyticum* isolates revealed that all were susceptible or had intermediate susceptibility to chloramphenicol, tetracycline, and vancomycin and most were susceptible to enrofloxacin. Thickening of the bladder wall and accumulation of sediment were common ultrasonographic findings. Contrast radiography or cystoscopy revealed findings consistent with encrusting cystitis in 3 dogs. Infection resolved in 2 dogs following surgical debridement of bladder plaques and antimicrobial administration. In 2 other dogs and 1 cat treated with antimicrobials, infection with *C urealyticum* resolved, but urinary tract infection with a different bacterial species developed.

**Conclusions and Clinical Relevance**—Results suggest that preexisting urinary tract disorders are common in dogs and cats with *C urealyticum* infection. Treatment with appropriate antimicrobials in combination with surgical debridement might eliminate *C urealyticum* infection. (*J Am Vet Med Assoc* 2005;226:1676–1680)

*Corynebacterium urealyticum* is a nonhemolytic, gram-positive, aerobic, rapid urea-splitting, non-spore-forming bacillus that was formerly known as *Corynebacterium* group D2.<sup>1</sup> Although *Corynebacterium* spp are an uncommon cause of lower urinary tract

infections in dogs and cats,<sup>2,3</sup> when *C urealyticum* infection does occur, it typically is associated with severe clinical signs and is difficult to treat.<sup>4,6</sup> In human medicine, *C urealyticum* urinary tract infection is most commonly found in patients who have previously undergone urologic procedures or had preexisting abnormalities of the bladder mucosa. Owing to its urease-producing activity, *C urealyticum* is associated with struvite and calcium phosphate precipitation, which can result in bladder wall encrustations, commonly referred to as encrusting cystitis.<sup>7,8</sup> Encrusting cystitis can involve the urethra, bladder, ureters, or renal pelvises.<sup>7</sup> Treatment for human patients with *C urealyticum* urinary tract infection is challenging and often requires surgical intervention or intravesicular treatment in addition to systemic administration of appropriate antimicrobials.

Little is known about the clinical features of *C urealyticum* urinary tract infection in dogs and cats or the outcome of treatment. The purposes of the study reported here were to identify clinical features of *C urealyticum* urinary tract infection in dogs and cats, including the outcome of treatment, and determine antimicrobial susceptibility patterns of *C urealyticum* isolates.

## Criteria for Selection of Cases

Medical records of all dogs and cats examined at the University of California Veterinary Medical Teaching Hospital between 1996 and 2003 for which results of bacterial culture of a urine sample were positive for *C urealyticum* were reviewed. Because *Corynebacterium* isolates obtained from animals were not routinely subtyped prior to 1996, dogs and cats examined prior to this time were not considered for inclusion in the study.

## Procedures

Information obtained from the medical records included signalment, history, physical examination findings, results of laboratory testing and diagnostic imaging, results of bacterial culture, treatment, and outcome. Only results of bacterial culture of urine samples obtained by means of antepubic cystocentesis were recorded.

**Bacterial culture procedures**—Urine samples were plated on sheep blood agar and MacConkey agar<sup>a</sup> plates by use of a quantitative loop method with a loop calibrated to deliver 0.01 mL. Alternatively, a semi-quantitative method was used if urine sediment was submitted. Plates were incubated in 5% CO<sub>2</sub> at 37°C and examined for growth daily for 5 days. Colony morphology was observed and quantified or semi-quantified according to standard laboratory protocols.

**Antimicrobial susceptibility testing**—Isolates from clinical cases, along with previously lyophilized

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unsubtyped isolates of *Corynebacterium* spp obtained from canine urine samples collected between 1977 and 1995, were examined and, if subtyped as *C urealyticum*, tested for antimicrobial susceptibility. A microbroth dilution assay<sup>b</sup> with a customized panel of antimicrobials was used for antimicrobial susceptibility testing. The standard panel consisted of amoxicillin-clavulanic acid, ampicillin, cephalexin, chloramphenicol, enrofloxacin, tetracycline, and trimethoprim-sulfonamide. A second panel was used to test for vancomycin susceptibility of some isolates because of the resistance pattern obtained. An isolate was considered susceptible if the **minimum inhibitory concentration (MIC)** was less than the published breakpoint concentration,<sup>9</sup> of intermediate susceptibility if the MIC was equal to the published breakpoint concentration, or resistant if the MIC was greater than the published breakpoint concentration. An isolate was considered multidrug resistant if it was found to be resistant to  $\geq 4$  antimicrobials.

## Results

Five dogs and 2 cats met the criteria for inclusion in the study. The dogs were a 14-year-old spayed female Doberman Pinscher mix, a 1-year-old spayed female Alaskan Husky mix, a 3-year-old spayed female Bichon Frise, a 7-year-old castrated male German Shepherd Dog mix, and a 6-month-old castrated male German Shepherd Dog mix. Mean age was 6.2 years. Mean body weight was 25.5 kg (56 lb; range, 7.4 to 40.6 kg [16 to 89 lb]).

The cats were both castrated male domestic shorthairs. One was 4 years old and weighed 2 kg (4.4 lb); the other was 10 years old and weighed 6.2 kg (13.6 lb).

Abnormalities reported by the owners included hematuria (n = 6), stranguria or pollakiuria (5), and urinary incontinence (4). In all 7 animals, urinary tract infection caused by an organism other than *Corynebacterium* spp had been diagnosed at least twice during the preceding 12 months, and all had been treated with at least 2 antimicrobials, including cephalexin, enrofloxacin, ampicillin, amoxicillin-clavulanic acid, metronidazole, clindamycin, and trimethoprim-sulfonamide. Two dogs and 1 cat had received prednisone prior to referral. In addition to previous urinary tract infection, 6 of the 7 animals had a history of micturition disorders prior to identification of *C urealyticum* urinary tract infection. Two dogs had a history of chronic urinary incontinence, 1 had a history of multifocal myelopathy and urine retention that required placement of a cystostomy tube for urine evacuation, and 1 had a history of pelvic fractures following automobile trauma and had required multiple urinary catheterizations. Both cats had had urinary catheters placed twice for urethral obstruction suspected to have developed secondary to idiopathic cystitis. One cat had developed an atonic bladder requiring manual expression by the owner, and perineal urethrostomy had been performed after the second episode of obstruction.

Physical examination findings were typically unremarkable, although 1 dog had a fever (rectal temperature, 39.8°C [103.6°F]) and a hypoplastic vulva. Complete blood counts and serum biochemical profiles revealed mild nonspecific abnormalities, except that 1 dog had a total WBC count of 51,630 cells/ $\mu$ L (reference

range, 6,000 to 13,000 cells/ $\mu$ L) with pronounced neutrophilia (43,214 cells/ $\mu$ L; reference range, 3,000 to 10,500 cells/ $\mu$ L). None of the animals were azotemic.

Results of urinalyses performed at the same time urine samples were submitted for bacterial culture were available for all 7 animals. Median pH was 8.0 (range, 6.5 to 9.0), and median specific gravity was 1.026 (range, 1.010 to 1.053). All animals had proteinuria, 1 cat had glucosuria, and 4 dogs and both cats had hemoproteinuria, as determined by means of dipstick analysis. Four dogs and 1 cat had pyuria, with urine WBC counts ranging from 5 to > 100 WBCs/hpf, and all 5 dogs and 1 cat had RBCs visible in the urine sediment. Three dogs and both cats had struvite crystalluria. Gram staining of the urine sediment revealed gram-positive rods in 3 dogs and both cats.

For all 7 animals, aerobic bacterial culture of urine samples yielded *C urealyticum*. However, antimicrobial susceptibility testing could be performed on only 4 isolates (all 4 were from dogs) because of slow growth of the remaining isolates in vitro. All 4 isolates were susceptible to tetracycline and chloramphenicol, 1 was susceptible to trimethoprim-sulfonamide, and 1 was of intermediate susceptibility to enrofloxacin. Two of the 4 isolates were tested for susceptibility to vancomycin, and both were found to be susceptible. All 4 isolates were resistant to amoxicillin-clavulanic acid, ampicillin, and cephalexin; 3 isolates were resistant to enrofloxacin; and 3 isolates were resistant to trimethoprim-sulfonamide.

Ten *Corynebacterium* isolates obtained from canine urine samples collected between 1977 and 1995 were subtyped as *C urealyticum* and tested for antimicrobial susceptibility. All 10 isolates had been obtained before or during surgical removal of urinary calculi; in all instances, calculi were identified as 100% struvite. All 10 isolates were susceptible to tetracycline and vancomycin and resistant to amoxicillin-clavulanic acid, ampicillin, and cephalexin. Nine were susceptible to enrofloxacin and 1 was resistant, and 9 were resistant to trimethoprim-sulfonamide and 1 was susceptible. All 10 were susceptible (n = 8) or of intermediate susceptibility (2) to chloramphenicol.

Abdominal radiography was performed in 2 dogs, and abnormalities (improper healing of pelvic bone fractures and diffuse heterogeneous mineralization within the urinary bladder) were identified in 1. Contrast radiography of the urinary tract (ie, excretory urography, double-contrast cystography, and retrograde urethrography) was performed in 2 dogs, and bilateral hydroureter and cystic radiopaque filling defects were seen in both (Figure 1). The dog with previous pelvic bone fractures also had marked dilatation of the urethra with filling defects.

Abdominal ultrasonography was performed in all 7 animals. Abnormalities included thickening of the urinary bladder wall (n = 6), moderate to marked accumulations of echogenic debris within the urinary bladder (5), hydroureter (3), unilateral renal pelvic dilatation (2), and hyperechoic bands across the bladder lumen (1). Computed tomography was performed in 1 dog; no clinically important findings other than unilateral ectopic ureter were identified. Cystoscopy was

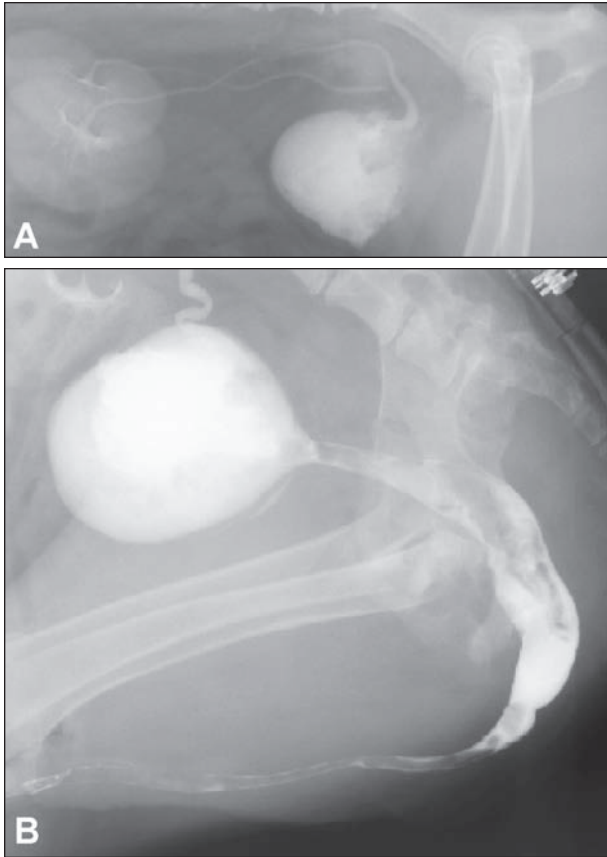


Figure 1—Lateral radiographic projections of the caudal portion of the abdomen and pelvis in 2 dogs with *Corynebacterium urealyticum* urinary tract infection. A—Radiographic projection obtained following excretory urography and positive-contrast cystography. Notice the large filling defect in the trigone region of the bladder and the bilateral ureteral dilatation suggestive of ureteritis. B—Radiographic projection obtained following excretory urography and positive-contrast retrograde cystourethrography. Notice the marked dilatation of the urethra and the urethral filling defects. Cystoscopy revealed encrusting urethritis and cystitis.

performed in 2 female dogs and 1 male dog. In all 3, the urethral and bladder mucosa appeared erythematous, and firmly adherent white or yellow plaques were seen on the mucosal surface. Hyperechoic bands spanning the bladder lumen that were seen during ultrasonography in 1 dog were identified as bands of encrusting debris during cystoscopy.

Surgery was performed in 4 dogs. An ectopic ureter was repositioned in 1 dog, a nonpatent cystostomy tube was replaced in a second dog, and plaques seen during cystoscopy were débrided in the other 2 dogs. Plaque material from 1 dog was submitted for analysis and was found to consist of an outer surface of 100% struvite and an inner core of 50% calcium phosphate and 50% struvite. Histologic examination of biopsy specimens of the bladder mucosa from 2 dogs revealed severe, suppurative, necrotizing, ulcerative cystitis with mineralization along the mucosal surface (Figure 2).

Five animals were treated empirically with antimicrobials before *C urealyticum* infection was documented. Amoxicillin-clavulanic acid (10.9 and 31.25 mg/kg [4.9 and 14.2 mg/lb], PO, q 12 h) was used in 2

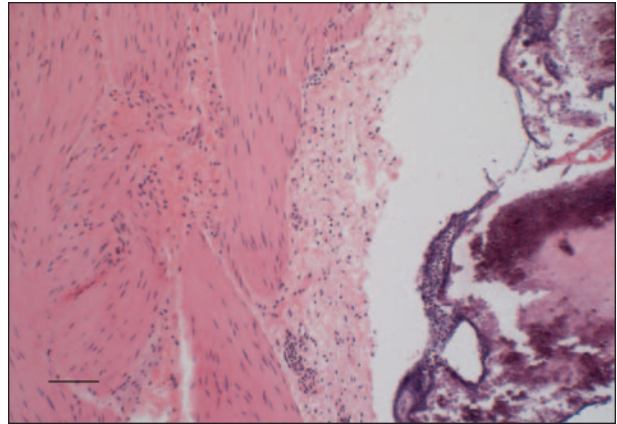


Figure 2—Photomicrograph of a section of the urinary bladder from a dog with *C urealyticum* cystitis. Transitional epithelium overlying the smooth muscle is completely denuded and replaced by a thick mat of partially mineralized (basophilic) degenerate cellular debris and fibrin exudates. H&E stain; bar = 100  $\mu$ m.

animals, ampicillin (17.2 mg/kg [7.8 mg/lb], PO, q 8 h) was used in 1, enrofloxacin (5.2 mg/kg [2.4 mg/lb], PO, q 12 h) was used in 1, and amoxicillin (16.1 mg/kg [7.3 mg/lb], PO, q 8 h) was used in 1.

Following identification of *C urealyticum* infection, 2 dogs were treated with doxycycline (6.8 and 7.5 mg/kg [3.1 and 3.4 mg/lb], PO, q 12 h). One of these was the dog with pelvic fractures. All clinical signs except for urinary incontinence resolved after the initial 2 weeks of an 8-week course of doxycycline treatment, but the dog was lost to follow-up after this time. In the other dog treated with doxycycline, *C urealyticum* infection persisted, and the dog was ultimately treated with vancomycin (14.3 mg/kg [6.5 mg/lb], IV, q 12 h). Clinical signs resolved following treatment with vancomycin, and bacterial culture of 3 serial urine samples did not yield any growth. The dog remained free from clinical signs of disease 1 year later. The dog that underwent surgical correction of an ectopic ureter was treated with amoxicillin-clavulanic acid. Bacterial culture of a follow-up urine sample did not yield *C urealyticum* but was positive for *Escherichia coli*. In the dog with multiple myelopathy and a cystostomy tube, clinical signs of lower urinary tract infection never resolved, and *C urealyticum* or multiple other pathogenic organisms were obtained from serial ( $n = 4$ ) follow-up urine samples obtained during the subsequent 2 years. This dog was treated with 4 different antimicrobials, but was never treated with vancomycin. The remaining dog, which was also determined to have vaginal carcinoma, was lost to follow-up.

One cat was treated with amoxicillin. Bacterial culture of a follow-up urine sample did not yield *C urealyticum* but was positive for *Proteus* spp. The other cat, which was the one with an atonic bladder, was euthanatized within 2 weeks after being discharged from the hospital.

## Discussion

*Corynebacterium urealyticum* is considered to be a commensal organism of the skin in human beings and has been identified on between 12% and 30% of individuals.<sup>7</sup> The source for dogs and cats is less clear, despite previous attempts to isolate the organism from the skin of dogs,<sup>6</sup>

but *Corynebacterium* spp have been reported to be part of the normal flora of the genital tract of cats.<sup>10</sup> As in humans, micturition problems and repeated catheterization in conjunction with concurrent antimicrobial administration could allow colonization of the bladder with this organism in dogs and cats. All of the animals in the present study had a predisposing factor that may have been involved in the development of *C urealyticum* infection. Previous reports<sup>4,6</sup> of dogs with *C urealyticum* infection have also identified predisposing factors, such as neurologic dysfunction and pelvic trauma. Correction of predisposing factors is thought to be essential in long-term cure of persistent or recurrent urinary tract infections.<sup>11,12</sup> Unfortunately, several of the animals in the present study had micturition abnormalities that were not amenable to surgical or medical correction. Thus, the overall prognosis for resolution of urinary tract infection was guarded.

Dogs and cats in the present study had several urinalysis abnormalities common to *C urealyticum* urinary tract infection. Most importantly, the urine was typically alkaline with 5 of the 7 animals having a urinary pH  $\geq 8.0$ . In addition, struvite crystalluria was common, along with pyuria and bacteriuria. Other urease-producing bacteria, such as *Staphylococcus* spp and some strains of *Proteus mirabilis*, are more common causes of alkaline urine and struvite crystalluria and urolithiasis in dogs.<sup>13</sup> However, adherent bladder mucosal plaques are typically not identified in dogs with urinary tract infections caused by these organisms. Persistent bacteriuria with alkaline urine and struvite crystalluria in the face of antimicrobial administration should raise the suspicion for *Corynebacterium* infection, as most *Staphylococcus* and *Proteus* organisms that cause urinary tract infection are susceptible to common antimicrobials.

Encrusting cystitis was identified in 3 of 5 dogs in the present study. Unlike urinary calculi, encrusting cystitis may have a variable echotexture and shape during ultrasonography, appearing as sediment along the mucosal surface that typically does not move as the patient is rotated. In humans, the radiographic, ultrasonographic, and computed tomographic characteristics of encrusting cystitis and pyelitis have been described, with computed tomography considered the most sensitive imaging method.<sup>14</sup> An alternative means of identifying encrusting cystitis is cystoscopy, with white plaques and visible struvite formations reportedly highly specific for *C urealyticum* infection in humans. The time required to develop encrusting cystitis in small animals is unknown, but the lack of struvite crystalluria in 2 animals in the present study may be attributable to a shorter duration of infection. Although detailed medical records were unavailable for the 10 isolates from urine samples obtained prior to 1996, it was known that the isolates came from dogs with struvite urolithiasis, providing further support for an association between *C urealyticum* infection and struvite calculi or encrusting cystitis. Mineralization of the bladder wall and struvite calculi are not 100% sensitive or specific for *C urealyticum* infection, but if encrusting cystitis is observed, *C urealyticum* infection should be considered.

*Corynebacterium urealyticum* isolates from human patients reportedly grow slowly in vitro, often requiring

48 to 72 hours before the organism can be identified.<sup>8</sup> Selective and specific culture media have been recommended to achieve rapid identification.<sup>15</sup> Because this pathogen is uncommon in small animals, the extra expense associated with routine use of selective media for bacterial culture of urine samples is probably unwarranted. But because growth of the organism was delayed for all animals in the present study, plates should be incubated and monitored daily for at least 3 to 4 days to aid identification. The longer incubation period is especially important for samples from animals with alkaline urine, encrusted cystitis, struvite calculi, micturition abnormalities, or a history of previous urologic procedures or recurrent urinary tract infections and previous antimicrobial use. Encrusted pyelitis secondary to *C urealyticum* infection has been identified in human patients that have undergone renal transplantation and are receiving immunosuppressive treatment.<sup>16</sup> Although none of the animals in the present study were transplant recipients, the increasing frequency of renal transplant procedures and therapeutic immunosuppression in cats and dogs makes monitoring urine samples prudent. The requirement for prolonged culture has led to the development of a polymerase chain reaction-based assay to detect *C urealyticum* infection in humans,<sup>17</sup> and this technique may become useful in small animal patients also.

One difficulty in treating *C urealyticum* infection is the multidrug resistant nature of the pathogen, resulting in limited antimicrobial choices.<sup>18,19</sup> Surprisingly, *C urealyticum* is generally resistant to penicillins even though it is a gram-positive organism. In fact, the MIC of amoxicillin-clavulanic acid for isolates in the present study was much higher than the mean urine concentration that can be achieved with this antimicrobial. A pattern of multidrug resistance was evident in previous reports<sup>4,5</sup> of dogs with *C urealyticum* infection, in which treatment was successful only after administration of teicoplanin, a vancomycin-related glycopeptide antimicrobial. Similar resistance patterns have been identified in other studies,<sup>18,20</sup> with most *C urealyticum* isolates found to be susceptible to glycopeptide antimicrobials and tetracyclines and only variably susceptible to fluoroquinolones. Tetracyclines were used with success in initial reports of humans with alkaline-encrusting cystitis,<sup>8</sup> but glycopeptide antimicrobials currently appear to be the first-line treatment for human patients with *C urealyticum* infection.<sup>21</sup> A disadvantage of glycopeptide antimicrobials is the necessity for IV administration owing to poor absorption following oral administration. Although tetracyclines may have activity against *C urealyticum*, doxycycline may not be the best choice because less than 25% of this antimicrobial is excreted in the urine<sup>22</sup> and adequate urine concentrations may not be obtained. Two dogs described in the present report were treated with doxycycline; however, additional treatments (surgical debridement with or without vancomycin administration) were also used. There are infrequent reports of *C urealyticum* urinary tract infection in humans resolving following the use of inappropriate antimicrobials,<sup>19</sup> but the mechanism for this is unclear. In 2 animals described in the present report in which an antimicrobial considered to be inappropriate on the basis of

antimicrobial susceptibility patterns was used, bacterial culture of follow-up urine samples did not yield growth of *C urealyticum*. However, other urinary tract pathogens were isolated from both of these animals, and the inability to recover *C urealyticum* may have been a result of competition between bacterial species either in vivo or in vitro. Another important finding is the apparent change in susceptibility to fluoroquinolones seen between *C urealyticum* isolates recovered from clinical cases in the present study and isolates obtained from urine samples collected prior to 1996. This may represent an important development of resistance since the FDA approved the use of enrofloxacin in the late 1980s. Variable susceptibility to fluoroquinolones has been recognized in isolates from humans as well.<sup>8,19</sup> Considering this change in susceptibility patterns, treatment should be selected on the basis of the most recent antimicrobial susceptibility patterns available.

In addition to antimicrobial administration, treatment options for *C urealyticum* cystitis include urine acidification and debridement of encrusting plaques. Urinary acidification was not a part of the treatment regimen in the animals described in the present report, but has been attempted in dogs and humans.<sup>4,5,23</sup> Adverse effects are common in humans and include tremors and anemia. Intravesicular administration of acidifying solutions, such as Suby solution G, has also been attempted in humans<sup>7</sup> and may be an alternative for animals not responding to antimicrobial treatment.

Debridement of plaques is often thought to be a necessary part of treatment regimen, as these struvite formations harbor bacteria and are suspected to prevent antimicrobial penetration.<sup>7,21,24</sup> The 2 dogs in the present report in which debridement was combined with antimicrobial administration both had successful outcomes.

*Corynebacterium urealyticum* is a rare cause of urinary tract infections in dogs and cats and, as evidenced by cases described in the present report, is most likely to be a problem in animals with preexisting lower urinary tract abnormalities. Clinicians should consider *C urealyticum* infection as a possibility in such patients, especially if alkaline urine and struvite crystalluria are present. In these cases, bacterial cultures of urine samples should be monitored and evaluated for at least 3 days. Cystoscopy was helpful in 3 animals in the present report, as it allowed documentation of the encrusting lesions commonly seen with this pathogen. Although antimicrobial treatment should be guided by results of susceptibility testing, tetracyclines, chloramphenicol, and possibly fluoroquinolones appear to be good initial choices. Debridement of mucosal plaques may be useful adjunctive treatments in patients with encrusting cystitis.

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